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A JOURNAL REPORTING THE PRACTICAL APPLICATION
OF OUR WORLD-WIDE KNOWLEDGE OF NUTRITION

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The American Journal of Clinical Nutrition

A JOURNAL REPORTING THE PRACTICAL APPLICATION OF OUR WORLD-WIDE KNOWLEDGE OF NUTRITION

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TREATMENT OF OBESITY WITH A LOW PROTEIN, CALORICALLY UNRESTRICTED DIET

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Weight loss has been successfully accomplished by reducing calories or by limiting carbohydrate. Here is proof that it can also be accomplished by limiting protein—which seems to effect a *voluntary* reduction of the caloric intake. While this intriguing mechanism is amply supported by the statistical evidence presented here, the authors are refreshingly candid in implying that hospitalization, supervision, and the role of routine are important contributing factors in the success achieved by a variety of reducing programs. In pondering the conflicting claims of the many reducing plans now preached and practiced, this thoughtful consideration of extra-dietary factors is most welcome.

NUTRITIONAL VALUE OF BEER WITH REFERENCE TO THE LOW SALT DIET

Edwin G. Olmstead, James E. Cassidy, and Francis D. Murphy 392

Physicians confronted with the wistful questions of hypertensives as to the legitimacy of "a few beers" will find these data on the average sodium content of American beer a helpful guide. Although alcoholic beverages are so much a part of the consumption pattern in the United States, careful analyses of their nutritional components are all too rare. This demonstration of the relatively low sodium content of beer represents a real contribution to our deficient knowledge in this field.

EFFECTS OF CHOLINE ON CARDIOVASCULAR LESIONS INDUCED BY FEEDING LARGE DOSES OF VITAMIN D

George F. Buckley and W. Stanley Hartroft 396

The idea that choline can protect against cardiovascular damage other than that caused by choline deficiency itself is a new one. This, however, is the implication of these studies of cardiovascular lesions in rats receiving excessive amounts of vitamin D. The effects of choline deficiency alone, and of choline deficiency coupled with hypervitaminosis D are compared, and the protective action of choline in both of these situations is demonstrated. The clinical lesson suggested by these novel findings is that lipotropic factors should be given to patients requiring massive doses of vitamin D.

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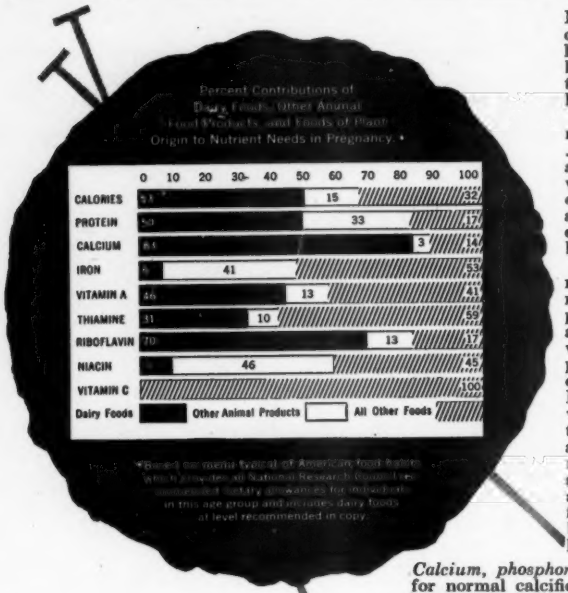
. . . *when the big problem is the* **LITTLE ONE!**



Every woman wants to give her child the best possible start in life . . . a wise choice of foods, before and during those important months of waiting, will help her achieve that goal.

Energy needs during pregnancy vary with the individual . . . intake should be only that amount which allows a normal weight gain. Generous amounts of high quality protein from animal sources—dairy foods, eggs, meat, fish, poultry—should be included in the diet.

Adequate levels of *fat* from natural fat sources should be maintained in the diet during pregnancy and lactation. Fat is a carrier of a number of factors which specifically influence reproduction, infant mortality, and child health. Vitamins A, D, and K have been shown to play a vital role in human reproduction.[1] Vitamin E,[1] essential fatty acids,[1] and a recently reported new fat soluble factor[2] are necessary for normal reproduction in animals. Most of these fat soluble factors are generously supplied by milk, butter, eggs, and green leafy and yellow vegetables.

Calcium, phosphorus, and vitamin D . . . required for normal calcification processes—must be supplied in generous quantities in the maternal diet. Vitamin D milk, cheese, and ice cream can provide the necessary amounts of these nutrients.

Riboflavin has been demonstrated as essential for birth of normal young of experimental animals. Dairy foods are a primary source of riboflavin. Deficiencies of *thiamine* and *iron* may occur during pregnancy. These nutrients will be supplied by frequent use of liver, other meats, eggs, vegetables, and whole grain or enriched cereals and breads. The daily consumption of citrus fruits, tomatoes, and other fruits and vegetables in generous servings will insure an adequate intake of *vitamin C*, and contribute *vitamin A* and other vitamins in lesser amounts.

One to one and one-half quarts of milk per day, or its equivalent in other dairy foods—cheese, butter, ice cream—are recommended for women during pregnancy, and may be further increased during lactation.

The presence of this seal indicates that all nutrition statements in the advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

1. Toverud, K. V., Stearns, G., and Macy, I. G.: Maternal Nutrition and Child Health. Bulletin No. 123, National Research Council, Washington, D. C. (Nov.) 1950.
2. Keane, K. W., Cohn, E. M., and Johnson, B. C.: Reproductive failure of rats on glyceryl trilaurate-containing diets and its prevention by certain natural fats. J. Nutr. *45*:275 (Oct.) 1951.

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NITROGEN BALANCE AS RELATED TO CALORIC AND PROTEIN INTAKE IN ACTIVE YOUNG MEN

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The literature on protein utilization during caloric restriction is here carefully reviewed, with special attention to studies carried out under military auspices which have not been widely accessible to the civilian medical reader. The futility of supplying a large number of calories in the absence of dietary protein, and of supplying excessive protein when the caloric intake is entirely adequate is one of the interesting points made. From the data examined, a formula is derived for a basic 500-calorie "food unit" which would be useful in any emergency feeding program, military or civilian.

EFFECT OF HIGH PLANT PROTEIN REGIMENS ON THE LIVER OF DOGS

E. Aubertin, J. Rivière, P. Loiseau, P. Debot, and R. Malineau 413

Laudable efforts have been made to find low-cost, readily available substitutes for the relatively expensive animal proteins. The virtues of soybean proteins, for example, have been the subject of numerous studies. That caution must always accompany enthusiasm is implied in this report of experiments in dogs (and humans) on high plant protein regimens. It is unfortunately apparent that the proteins of such plants as soybeans, peanuts, and sunflower can be consumed in only limited amounts if serious repercussions on the liver are to be avoided. These repercussions have been documented by French workers and are reported here, with appropriate warnings against the incorporation of large amounts of these plant proteins in the diet of humans, especially of patients with liver disease.

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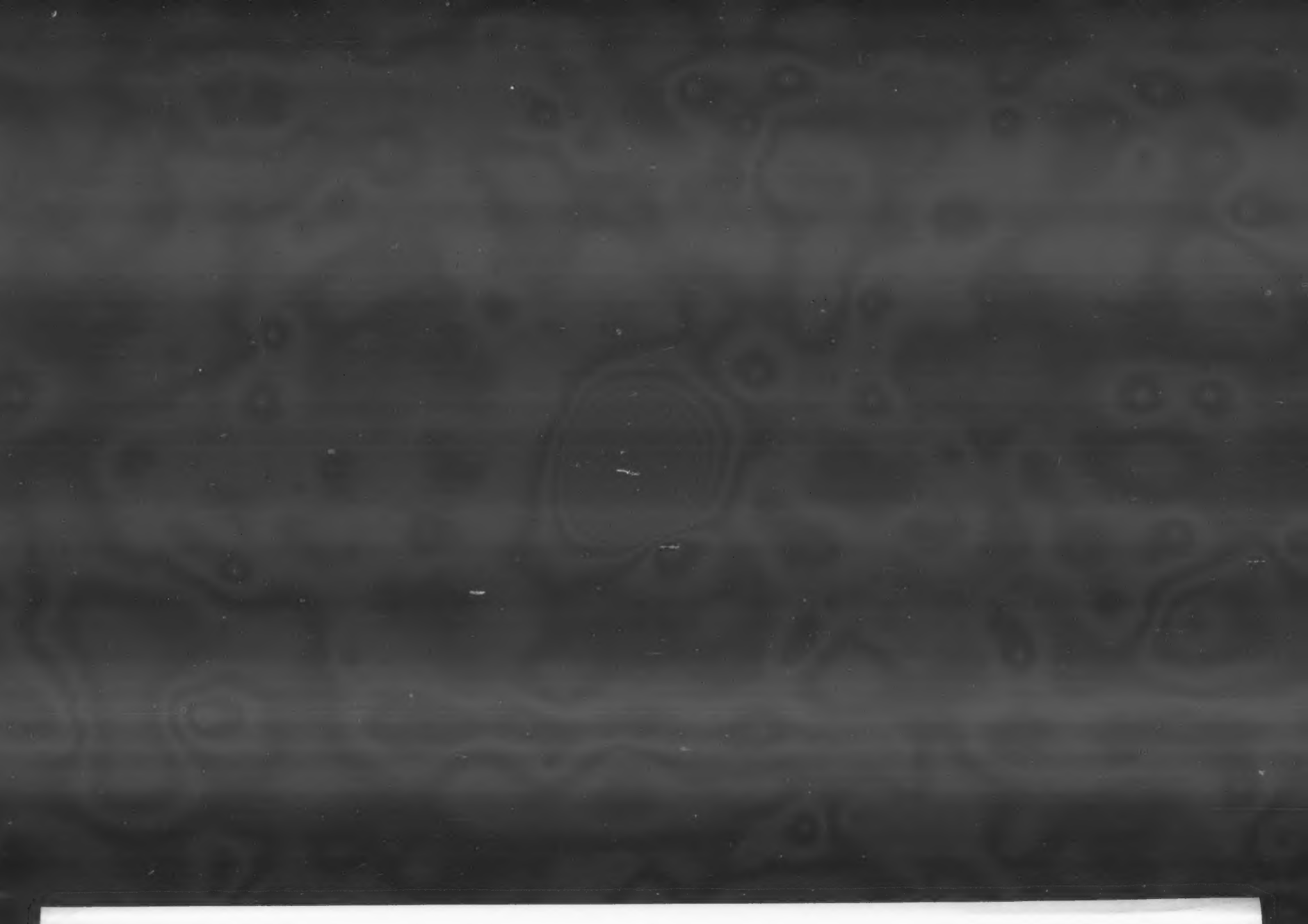

The American Journal of Clinical Nutrition

NOVEMBER–DECEMBER 1954 VOLUME 2, NUMBER 6

Treatment of Obesity with a Low Protein Calorically Unrestricted Diet

By VINCENT P. DOLE, M.D.,* IRVING L. SCHWARTZ, M.D.,† JØRN HESS THAYSEN, M.D.,‡ NIELS A. THORN, M.D.,‡ AND LAWRENCE SILVER, M.D.§

THIS REPORT evaluates immediate and late results obtained in the treatment of 42 obese patients. The diet limited protein to 35 ± Gm./day, but provided a surplus of carbohydrate and fat, and permitted each patient to regulate his own caloric intake. Protein was added to the diet during control periods in order to test the specific action of this nutrient without a change in other conditions of treatment.

Prior work in a number of clinics has shown that the low sodium diets used in the treatment of hypertension usually cause a loss of weight even when calories are unrestricted.[1–8] We became interested in this phenomenon, and found that salt, when added to a low sodium diet, had no effect on the weight loss, although it did prevent the expected fall of blood pressure. Protein, on the other hand, arrested the weight loss and allowed the blood pressure to fall.[9]

The antihypertensive and the appetite-depressing effects of the diet thus seemed to be separable, and it became of interest to consider the value of restricting proteins in the treatment of obesity.

From the Hospital of the Rockefeller Institute for Medical Research.

* Member, The Rockefeller Institute for Medical Research and Physician to the Hospital.

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§ Visiting Investigator, The Rockefeller Institute for Medical Research and Assistant Physician to the Hospital. Postdoctorate Fellow of the National Institutes of Health.

SUBJECTS

Apart from obesity, all of the 42 patients had been in good health and actively at work before admission. Those treated in the clinic continued at their jobs—some at fairly hard factory labor.

Table I and Figure 1 show the distributions of age, sex, and degree of obesity. Almost all of the patients had failed in attempts to lose weight at home, and thus were a selected group, willing to accept the discipline of a metabolic study.

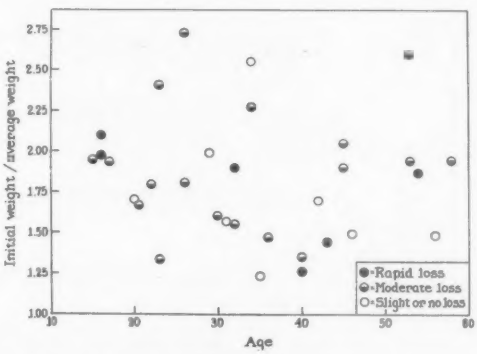

Fig. 1. Lack of correlation between initial response and the age and degree of obesity. Losses above 200 Gm./day are rated as rapid, 100–200 Gm./day as moderate, and below 100 Gm./day as insignificant.

TABLE I

Results of Treatment

Distribution of patients					Results under treatment						Results after discharge					Significant loss of weight	
					Weight loss on:												
Group	Patient (RIH unit number)	Sex	Age	Initial obesity: Initial wt./average wt.	Supplemental diet	Basal diet	Nature of protein supplement: Source	Protein	Calories		Weight at discharge	Period without supervision	Weight at follow-up	Change	Final obesity: Follow-up wt./average wt.	Immediate response	Follow-up
			Yrs.		*Gm./day*	*Gm./day*	*Gm./day*	*Gm./day*	*Cal./day*		*Kg.*	*Mos.*	*Kg.*	*Kg.*			
A	13917	F	26	2.73	−100	−140	Beef	200	46	230						x	
	12457	F	53	2.59	0	−150	Beef	200	46	230	144.3	12	175.0	+30.7	2.74	x	
	13955	F	34	2.56	0	−225	Beef	200	46	230	143.4	12	138.6	−4.8	2.37	x	
	13970	F	29	1.98	+70	−100	Lesofac	92	46	368	—	—	—	—	—	x	
	13737	F	53	1.94	−30	−180	Beef	200	46	230	112.6	14	117.9	+5.3	1.94	x	
	13828	F	58	1.93	0	−120	Beef	200	46	230	106.7	12	104.9	−1.8	1.78	x	
	13735	M	32	1.90	0	−350	Beef	200	46	230	139.0	13	148.6	+9.6	1.95	x	
	14097	F	45	1.90	−160	−250	Beef	200	46	230	110.7	8	130.0	+19.3	1.95	x	
	14210	F	20	1.71	−60	−80	Lesofac	92	46	368	92.0	1	94.0	—	—		
	13914	F	41	1.70	0	−80	Beef	200	46	230	105.5	6	109.0	+3.5	1.72		
	14150	F	31	1.57	0	−20	Beef	200	46	230	90.3	8	90.0	−0.3	1.54		
	13988	M	32	1.56	+140	−200	Beef	413	96	475	93.1	4	105.6	+12.5	1.50	x	
	14030	F	46	1.49	−50	0	Lesofac	92	46	368	—	—	—	—	—		
	13973	F	36	1.45	−130	−70	Beef	200	46	230	81.5	10	78.9	−2.6	1.26	x	x
	13833	F	40	1.35	0	−135	Beef	200	46	230	82.4	2	80.9	−1.5	1.26	x	x
	13948	M	40	1.26	−260	−400	Lesofac	140	70	520	106.8	17	127.1	+20.3	1.32	x	
	Mean	0.81 F	39	1.86	−36	−156											
	S. D.		±11	±0.43	±94	±110											
	S. D. of mean				±23	±28											
B	13952	F	23	2.41	−200		Beef	200	46	230	115.3	3	119.2	+3.9	2.02	x	x
	14389	F	16	2.10	−320		Lesofac	92	46	368	—	—	—	—	—	x	
	13885	F	45	2.05	−200		Beef	200	46	230	—	—	—	—	—	x	
	13686	M	15	1.95	−200		Beef	200	46	230	120.4	3	125.3	+4.9	1.94	x	
	14390	F	17	1.87	−140		Lesofac	92	46	368	—	—	—	—	—	x	
	13921	F	30	1.65	−100		Beef	200	46	230	97.3	4	93.2	−4.1	1.53	x	
	Mean	0.83 F	24	2.00	−193												
	S. D.		±12	±0.27	±75												
	S. D. of mean				±30												

Distribution of patients					Results under treatment					Results after discharge					Significant loss of weight	
					Weight loss on:											
Group	Patient (RIH unit number)	Sex	Age	Initial obesity: Initial wt./average wt.	Supplemental diet	Basal diet	Nature of protein supplement: Source	Protein	Calories	Weight at discharge	Period without supervision	Weight at follow-up	Change	Final obesity: Follow-up wt./average wt.	Immediate response	Follow-up
			Yrs.		*Gm./day*	*Gm./day*				*Kg.*	*Mos.*	*Kg.*				
C	13710	F	34	2.27		−100				131.6	15	141.0	+9.4	2.34	x	
	13591	M	16	1.93		−500				141.1	12	136.3	−4.8	1.78	x	
	13886	F	54	1.87		−280				97.3	12	109.0	+11.7	1.93	x	
	13830	F	26	1.81		−180				101.0	12	103.5	+2.5	1.66	x	
	13618	M	21	1.79		−150				96.1	15	105.3	+9.2	1.71	x	
	13730	F	19	1.68		−100				—	—	—	—	—		
	13764	F	56	1.48		−50				96.3	16	88.3	+2.0	1.48	x	
	13662	F	43	1.44		−250				69.4	12	61.3	−8.1	1.10	x	x
	13922	F	23	1.33		−100				74.6	12	74.8	+0.2	1.17	x	x
	13884	F	35	1.23		−75										
	Mean	0.80 F	33	1.68		−179										
	S. D.		±14	±0.32		±85										
	S. D. of mean					±27										
D	13864	M	23	1.51		−146				98.4	14	100.2	+1.8	1.51	x	
	13863	M	35	1.49		−182				97.0	14	99.2	+2.2	1.45	x	
	13862	F	23	1.39		−109				92.9	14	104.2	+11.3	1.52	x	
	13861	M	39	1.23		−192				70.0	14	70.0	0	1.15	x	x
	13860	F	53	1.22		−55				85.6	14	87.9	+2.3	1.23		
	13859	F	50	1.18		0				77.4	14	79.2	+1.8	1.21		
	13866	F	50	1.03		−36				76.5	14	79.2	+2.7	1.05		
	g	M	28	1.15		−215				71.9	15	68.7	−2.8	1.02	x	x
	d	M	40	1.12		−202				82.0	21	82.0	0	1.03	x	x
	s	M	61	1.10		−195				83.4	15	82.9	−0.5	1.01	x	x
	Mean	0.40 F	40	1.24		−137										
	S. D.		±13	±0.17		±121										
	S. D. of mean					±38										

Physical examinations, x-ray of chest, urinalysis, and measurements of hemoglobin and plasma protein[10] showed no important defects except for benign hypertension in seven patients. Further studies, made after admission of patients to the hospital, likewise proved normal: basal metabolic rate, urea clearance, bromsulfalein excretion,[11] thymol turbidity,[12] thymol flocculation,[13] and albumin-globulin ratio.[14] The uptake of radioiodine and the concentration of serum cholesterol were normal in two patients suspected of hypothyroidism.

Obesity was rated by the ratio between actual weight and the value reported to be average for a person of the given sex, age, and height.[15] This arbitrary index measures the excess of body fat in an approximate way,[16] but as a relative measure it appeared adequate. The patients were of average build and the index correlated with their appearance on physical examination; any other acceptable measurement of obesity would have ranked them in similar order.

Diet

The basal diet contained 35±5 Gm. protein per day, with unlimited carbohydrate, fat, and salt. Orange juice, coffee, and toast—one or two slices with butter and jelly—made a typical breakfast; an occasional patient took hot cereal and cream, but most preferred the smaller meal. Lunch consisted of meat or fish (about 10 Gm. protein), potato and another vegetable, one or two slices of bread, and fruit for dessert. Supper was comparable: egg, spaghetti, or small serving of meat (about 6 Gm. protein), potato and another vegetable, one slice of bread, salad with French dressing, fruit or cake for dessert. Fruit juice (150 cc.) was served at 10 a.m., 2 p.m., and 8:30 p.m. The timing of meals and the distribution of calories duing the day are shown in Figure 2.

To make certain that the patient had completely satisfied his appetite, the diet kitchen served a bowl of sugar, a dish of jelly, and a large section of butter on each tray, and weighed back the food not eaten. Rock candy was available on request but did not prove popular.

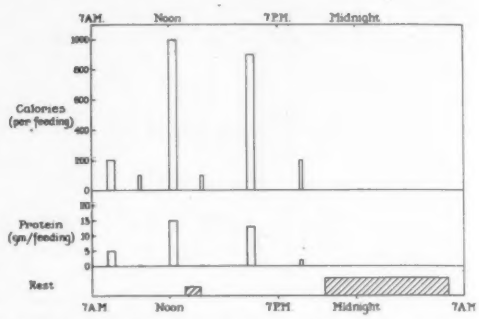

Fig. 2. Distribution of calories and protein during a hospital day.

As a control for the restriction of protein in the basal diet, supplementary protein was fed during periods of three to six weeks' duration in amounts sufficient to provide total intakes of 80 to 130 Gm. protein per day. In some cases lean beef was prescribed, replacing the much smaller servings of meat in the meals of the basal diet, while in other cases milk or Lesofac®* replaced the interim servings of fruit juice. In each instance the supplement contained more calories than the food it replaced: lean beef added 230–475 cal./day, and Lesofac, 368–520 cal., but the total intake of calories always could be determined by the patients. At most, the prescribed supplement accounted for 20 per cent of the total caloric intake.

The patients treated in the out-patient clinic received a mimeographed booklet outlining a simple version of the basal diet (Table II). They agreed to follow the schedule for one month, and to record in a notebook their morning weights, the type and amounts of food taken, and the time of eating.

Results

The patients may be divided into four groups, based on differences in treatment. *Group A*, composed of 16 subjects, received a high protein supplement for 3 to 6 weeks

* Lesofac (Wyeth), manufacturer's analysis as follows: Protein 50.0%, carbohydrate 39.2%, fat 1.0%, cholesterol 25 mg. %, ash 5.8% (including sodium 0.02, calcium 0.80, potassium 0.85, magnesium 0.10), moisture 4.0%, vitamin B_1 2 mg. %, vitamin B_2 4 mg. %, niacinamide 20 mg. %.

TABLE II

Diet for Out-patients

Breakfast	
Fruit juice	No limit
Choice of either:	
1. Hot or cold cereal	2 T
Cream	2 T
Toast	1 Sl
2. Toast	3 Sl
Butter, jam, sugar	
Coffee or tea	
Mid-morning	
Fruit juice	No limit
Noon Meal	
Vegetables	2 units*
Toast	1 Sl
Salad: Lettuce with tomato or fruit, and French dressing; no cheese	No limit
Butter, jam, sugar	No limit
Fruit for dessert	No limit
Coffee or tea	
Mid-afternoon	
Fruit juice	No limit
Evening Meal	
Soup	1 unit
Vegetable, egg or meat	2 units
Salad (as above)	No limit
Butter, jam, sugar	No limit
Fruit for dessert	No limit
Coffee or tea	
Before Bed	
Fruit juice	No limit

One unit of potato and one of green vegetable to be eaten each day; the remaining units may be chosen freely. Alcoholic beverages are not allowed. The body weight should be taken each day, preferably before breakfast, and a record of the diet kept in a notebook.

* Each of the following quantities is equivalent to one unit:

I. Vegetables

Artichoke	3 med.
Asparagus	20 stalks
Beans	3 T
String beans	1 C
Beets	1 C
Cabbage	2 C
Carrots	3 C
Cauliflower	3 C
Celery	50 stalks
Corn	1/2 C (1 ear)
Eggplant	2 Sl
Cooked greens	1 C
Salad greens	3 C
Mushrooms	2 C
Onions	3 C
Parsnips	2 C
Green peas	1/2 C
Potatoes (without skin)	3 med.
Pumpkin	3 C
Rhubarb	10 C
Rice (cooked)	3 C
Sauerkraut	2 C
Squash	2 C
Tomato	2 C
Turnip	3 C
Watermelon	5 C
Zucchini	2 C

II. Meat, Eggs, Cheese, Milk

Lean meat or fish	1 piece (2 x 2 x 1/4 in.)
Bacon	2 strips
Egg	1 small
Cheese	
American	1 piece (2 x 2 x 1/2 in.)
Cheddar	1 piece (2 x 2 x 1/2 in.)
Cottage	1 T
Cream	4 T
Parmesan	2 T
Swiss	1 piece (2 x 2 x 1/2 in.)
Milk	
Whole	1/2 C
Skim	1/2 C
Cream	1 C

III. Cereal Products

Macaroni, noodles, spaghetti (cooked)	1 C
Bread	2 Sl
Breakfast cereal	
Hot (cooked)	3 T
Ready to eat	1 T
Crackers	
Saltines, Graham, Cookies	5 dbl.

IV. Clear Soups

Asparagus	2 C
Bean	1/2 C
Beef	1/2 C
Celery	1 C
Chicken	1/2 C
Clam chowder	1/2 C
Consommé	1/2 C
Onion	1 C
Pea	1/2 C
Spinach	1 C
Tomato	1/2 C
Vegetable (vegetarian)	1 C

and basal diet alone for an additional 3 to 12 weeks. *Group B,* 6 patients, lost weight rapidly while receiving a supplement, and so was continued on the supplemented diet for the whole study. *Group C* consisted of 10 patients who were treated with basal diet alone for 2 to 12 weeks. *Group D,* 10 patients, was treated only in the clinic, using a simple version of the basal diet.

At the completion of their hospital treatment the patients in *Groups A, B,* and *C* received a copy of the clinic diet and instruction in its use. They were invited to return to the clinic at any time, but were given no systematic appointments. They did not anticipate the general follow-up study 3 to 12 months after discharge.

The patients in the hospital were weighed each morning after voiding and before breakfast. The scale, calibrated against standard weights, had an accuracy of ±100 Gm. Table I, summarizing the results, shows that 32 out of the 42 patients lost 100 or more Gm./day during the period of initial treatment. These responses are further analyzed in Figure 1 which shows their relation to age and degree of obesity. In this figure, a sustained loss at a rate of 200 Gm./day is rated rapid, 100–200 Gm./day, moderate, and below 100 Gm./day, insignificant. It will be seen that neither age nor degree of obesity made any difference in the initial rate of loss.

Hospitalization as a Cause of Weight Loss

Many patients lost weight during the control periods. They were allowed to eat freely, and were provided with an ample supply of all dietary essentials. Nevertheless, 4 of the 16 patients in *Group A,* and all 6 patients in *Group B,* lost more than 100 Gm. per day. They insisted they had enough to eat, and were unable—or unwilling—to eat enough to maintain a steady weight.

Although the quantity of food seemed adequate, the patients were aware of other kinds of limitation. The greatest of these was a change in the timing of meals. Like most fat persons, they tended to have poor appetites in the morning and to be hungry at night.[17] At home, many of them ate little or no breakfast, and often took a light lunch. They usually ate once or twice in midafternoon, choosing something like a sandwich or a milkshake, then ate a good supper, and continued to eat throughout the evening, especially before going to bed. In the hospital, they were compelled to follow a rigid schedule of eating which was far different from their usual habits (Figure 2).

It proved necessary to relax the schedule slightly in order to satisfy the patients. Most of them felt the evening glass of fruit juice was inadequate, and some threatened to leave unless extra food was made available at bedtime. Therefore, they were allowed to set aside bread from meals when it was in surplus, and hold it in reserve for the evening. The majority saved a slice of bread from lunch and buttered it heavily; some added an extra layer of jam. It relieved their distress at bedtime, and made them willing to stay—but undoubtedly the patients would have eaten more from the icebox at home.

Patients also noticed a change in the kind of food served: familiar, tasty foods were missing, and instead they received unlimited servings of vegetables and fruit. Calculated from dietetic manuals, the supplemented diets appeared to be fully adequate, but they stimulated no enthusiasm; the foods were not what the patients would have chosen for themselves. In addition, no alcohol was served in the hospital, whereas most patients had been accustomed to taking it in moderate amounts.

The importance of familiar food was illustrated by one patient in *Group B* (RIH 14389), a 17-year-old girl weighing 2.10 times the average for her age and height (Figure 3). Increase of the supplement, raising her intake of protein to 121 Gm./day, had no significant effect on her rapid loss of weight. She said that the hospital food was strange to her, and distasteful. More than anything else, she missed a special kind of rye bread that she ate at home. During the next period we obtained the familiar bread, and made it available without restriction. Immediately her consumption of food increased: she ate about 180 Gm. of rye bread per day, buttered

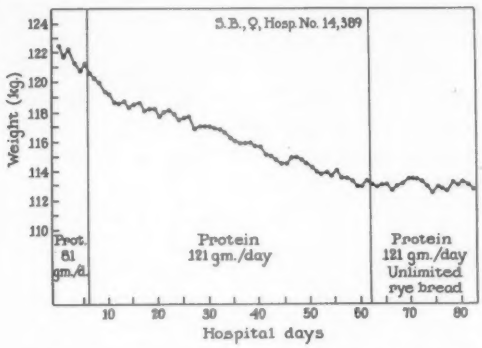

Fig. 3. Weight loss occurring on a liberally-supplemented diet. Note that the addition of rye bread in the third period stopped the loss.

heavily, and made sandwiches out of food that she had previously rejected. Her weight became steady, ending a downward trend of 62 days.

Specific Effect of Dietary Protein

In *Group A*, 14 of the 16 subjects responded to withdrawal of the supplement by an increased loss of weight (Table I). Appetite actually was reduced, since in the case of all 7 patients for whom detailed diet kitchen records were available, the voluntary intake of calories during the supplemented periods equaled or surpassed the intake during periods of basal diet alone. Addition of supplement not only provided calories by direct prescription, but also caused an increased consumption of nonprescribed food.

Limitation of protein caused a fairly consistent reduction of appetite, but the extent of reduction differed from patient to patient (Table I). On the supplemented diet, the subjects in *Group A* lost 36 ± 94 Gm./day, while on the basal diet alone they lost 156 ± 110 Gm./day. Despite these large standard deviations of response, the difference of means was statistically significant ($p < 0.01$)—a fact that is brought out more clearly by calculation of the standard deviations of the means (Table I).

Results in the Clinic

The average response to treatment of clinic patients during the first month equaled that shown by the patients in the hospital (Table I). After a brief effort, three women quit. The remaining seven patients made a serious effort to follow the instruction, and succeeded, as judged from their detailed notes and steady losses of weight. Social pressures and other practical inconveniences of a special diet gave some difficulty, but hunger was not a problem. The patients continued to work and reported normal vigor on the limited diet.

Follow-up Studies

All patients, when released from supervision, gradually modified their diets in the direction of previous patterns of eating. Many of them (52 per cent), abandoning control completely, ate and lived just as they had before treatment, and at follow-up were found to have returned to their original states of obesity (Table I). The minority of patients, 18 per cent of those followed, lost 2 Kg. or more during the interval after discharge. They had succeeded in fitting a low protein diet to their own schedules, or had used the diet periodically to check gains of weight; all of them said their habits of eating had been greatly changed by treatment. It is significant that the most intelligent subjects had the best results. Markedly obese patients continued to be overweight, but when the treatment reduced excess weight by 25 per cent or more, the patient usually improved in appearance and felt that the results justified the effort.

At the follow-up examinations 3 to 12 months following discharge 27 per cent (9/33) of the patients met this standard, the low percentage of success probably being due in part to the absence of regular medical supervision. Although more active management might have increased the percentage of good response, it is of interest to note that the diet alone enabled some patients to achieve control of appetite.

Normal Liver Function

The possibility of harm from restriction of protein must be considered. Recent work

TABLE III
Liver Function Tests

Patient (RIH unit number)	Days on low-protein diet	Bromsulfalein retention		Thymol		Protein	
		5 min.	45 min.	Turbidity	Flocculation	Total	A/G ratio
		%	%	*Units*	*Units*	*Gm./100 cc.*	
13952	0	53	6	5.2	0	8.70	2.0
	67	49	4	1.9	0	8.32	1.4
	148	56	4	3.3	0	—	—
13830	9	61	3	3.2	0	6.79	1.5
	87	66	3	2.5	0	6.48	2.5
	128	62	8	2.0	0	7.12	1.7
	152	54	3	2.7	0	7.66	1.8
13922	0	—	—	—	—	6.22	2.5
	42	56	3	2.7	0	7.74	2.8
	63	67	3	1.8	0	—	—
	119	47	1	3.0	0	7.33	2.8
12457	96	—	—	—	—	8.00	1.3
	115	41	7	2.2	0	—	—
	134	57	9	2.0	0	—	—
	141	52	10	2.3	0	—	—
	162	—	—	—	—	7.55	1.5

has emphasized the importance of dietary protein for maintenance of normal liver function.[18-21] Obese patients, with their greater liability to cirrhosis,[22] deserve special study in this connection, since it has been found that extreme and ill-advised reduction diets occasionally precede the onset of manifest cirrhosis.[23] It was reassuring, therefore, to find that patients treated with the low protein diet showed essentially normal excretions of bromsulfalein, normal thymol tests (turbidity under 5 units, no flocculation), and normal concentrations of plasma protein (Table III). The one patient with borderline retention of bromsulfalein (Patient 12457) showed no significant change during the period of observation.

Discussion

It is convenient to divide the possible variations of diet into two classes: those fixed by the experimenter, and those freely chosen by the patient. The first class of conditions leaves the subject no choice except to discontinue the treatment if he dislikes the conditions. A free variable, on the other hand, is neither imposed nor limited. It therefore reflects a free choice on the part of the patient, and if it is a quantitative variable like the caloric intake, it provides a numerical measure of the patient's response. In the present study, the amount of dietary protein had an arbitrarily established value, while the caloric intake was free to vary, just as it is in day-to-day living. Under the defined conditions of this study, the patients varied their own caloric intake in a predictable way in response to changes we made in the level of dietary protein.

In normal life, the obese patient lives under a different set of conditions from those established in the hospital, and responds to them by overeating. Ultimately, we can hope to understand the variety of metabolic and psychological causes behind his abnormal response,[24] and thus be able to cure the disease by specific treatment. Until then, it is important to discover what external conditions influence his diet, and perhaps by correcting certain habits make it possible for him to stabilize at a lower weight.

It is significant that most successful reducing diets include a ritual of fixed conditions—kind of food, time of meals, tempo of eating, exercise, early rising—in addition to caloric restriction. Some diets, such as the low carbohydrate diet of Pennington[25] and the low protein diet of the present study even dispense with caloric restriction altogether, and rely upon noncaloric limitations to pro-

vide an indirect control of intake. Evidently, the details of the routine are important. The present work started with the simple hypothesis that limitation of dietary protein could regulate appetite, and the results show this to be true. At the same time, the work made it clear that the original conception of a single, specific factor was too narrow, since the routine of treatment, as well as the limitation of protein, caused patients to lose weight. The importance of "routine" is apparent in the present work, and it should be considered in a theoretical analysis of any successful diet.[26]

Many years ago Chittenden[27] and Hindhede[28] showed that low protein diets, very similar to the one used in this study, supported young athletes in vigorous health. These careful investigators were so impressed with the good results of the diet that they adopted it for themselves. The fact that they outlived all their critics perhaps was a coincidence, but apparently they were not harmed by the restriction of protein. Strieck, more recently,[29] added to the evidence that 30 to 40 Gm. protein per day is adequate for healthy adult persons. Obese subjects, moreover, appear to have an exceptional ability to conserve body nitrogen,[30,31] presumably because of the protein sparing action of their body fat. Recognizing this fact, Møller[32] obtained excellent results in the treatment of obesity with a low protein, low calorie diet.

As a practical matter, the low protein diet with its accessory conditions offers a method for control of appetite after a successful reduction of weight. Caloric deficit, if it can be imposed, is the most direct and efficient way of reduction, but it is not suitable for the treated patient. The low protein diet, on the other hand, allows appetite to adjust caloric intake to expenditure and at the same time curbs the tendency to overeating. Like all other dietary treatment of obesity, this program is merely symptomatic: at best, it converts an obese patient to one who is potentially obese with a need for continuing medical supervision. When this is available, the low protein diet should prove a useful means of treatment.

Summary

A low protein, but calorically unrestricted, diet was used to treat 42 overweight patients. The immediate results were encouraging: 32 subjects lost 100 or more grams per day, and continued to feel well. After they were discharged, however, a majority of patients returned to their previous ways of eating. At follow-up examinations 3 to 12 months after discharge, it was found that 52 per cent of the patients had regained all of their original weight, 30 per cent had remained nearly steady, and 18 per cent had continued to reduce without supervision.

Prescription of a high protein supplement led to an increase in the voluntary consumption of *un*prescribed calories, thus suggesting that the limitation of protein to 35 ± 5 Gm/day actually had reduced appetite. In addition, the results indicated that the routine of treatment (scheduling of meals, restriction in choice of food, regulation of activities) contributed significantly to the control of appetite. The general health remained good, and liver function, as studied by serial tests, remained unchanged by treatment.

Limitation of protein appears to be a useful adjunct to the treatment of obesity; but, as with any other diet, regular medical supervision is essential. It offers a means of regulating appetite during the maintenance period that follows any successful course of reduction, and suffices as a sole measure of treatment for milder degrees of overweight.

Acknowledgment

We are indebted to Dr. Emma Kyhos (Hoffmann-LaRoche, Inc.) and Dr. Kenneth Thompson (Metropolitan Life Insurance Co.) for their interest in this study; a number of the patients were referred to us by them, and followed after discharge from our clinic.

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Resumen

Tratamiento de la obesidad con una dieta hipoproteica sin restricción calórica

Una dieta pobre en proteína, pero sin restricción calórica, fué empleada para tratar a 42 pacientes obesos. Los resultados inmediatos eran muy satisfactorios: 32 sujetos perdieron 100 o más gramos por día, y seguían gozando de bienestar. Sin embargo, despues de ser dados de alta, la mayoría de los pacientes volvieron a sus anteriores costumbres alimenti-

cias. Al ser nuevamente examinados, entre los 3 y 12 meses posteriores, un 52 por 100 de los pacientes habían ganado de nuevo su peso anterior, un 30 por 100 habían quedado más o menos estables, y un 18 por 100 habían continuado perdiendo peso sin ninguna supervisión.

La suministración de un suplemento rico en proteína provocó un aumento en el consumo voluntario de calorías no prescritas, indicando así que la restricción de la proteína a 35 ± gramos/día había, en efecto, reducido el apetito. Además, los resultados indican que la rutina del tratamiento (comidas a horas fijas, restricción en la selección de alimentos, regulación de las actividades) contribuyó significativamente al control del apetito. La salud general quedó bien, y la función hepática, revelada por pruebas consecutivas, quedó sin cambio durante el tratamiento.

La restricción de la proteína parece ser un muy útil adjunto al tratamiento de la obesidad; pero como con cualquier otra dieta, la supervisión médica es un concomitante esencial. El régimen ofrece un método para arreglar el apetito durante ese período de mantenimiento que sucede al éxito en todo curso de reducción, y es suficiente como único modo de tratamiento de los grados menores de sobrepeso.

Ordering the Disorder of Medicine

"The basic components of medical knowledge are water, electrolytes, oxygen, lipids, proteins, and carbohydrates. With organizing principles, working through certain mechanisms, the animal body can be compounded of these, and, in these terms, it can also be analyzed . . .

"Knowledge organized in such a way as to trace from the original chemical units of protoplasm the way in which nature has solved the problems of the functional needs of the body provides an intellectually economical schema that is just as usable at the bedside as in the classroom of the basic sciences. By being taught to think the same way in both branches of medicine, clinical and basic, the void between the two can be bridged; the 'common dilemma' has in these terms provided the means of relating the one with the other. Perhaps it is well, at times, to be caught on the horns of a dilemma in order to be shown the essential oneness of problems that at the onset seem to be multiple and widely disparate."

—Irvine H. Page. *Journal of the American Medical Association* 156: 111, 1954.

Specialization: Sign or Symptom?

"It is only natural that the opening up of so many new frontiers in medicine should have given rise to a far greater measure of specialization than ever before, and it is here that we should perhaps pause to reflect upon one of the lessons of past history, that overspecialization, particularly when based upon insufficient knowledge, has generally been the precursor of a period of decline and decadence. However valuable the role of the specialist may be, and none would be so foolish as to deny his vital function in the medical world, we should not let our regard for him blind us to the vital part played by the general practitioner who, though he cannot and does not claim to be an expert in every field, is yet most peculiarly qualified to be the guardian of his patient's health by reason of an intimate knowledge of his circumstances, environment and medical history, and most of all by virtue of the confidence that is placed in him as a result of long association."

—A. D. Trendall. *The Medical Journal of Australia* 41 (4): 120, 1954.

Nutritional Value of Beer *with Reference to the* Low Salt Diet

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THE PLACE of the low sodium diet in the treatment of congestive heart failure and of certain renal diseases has been well established, while the use of the low sodium diet in the management of hypertension is still a matter of controversy. A recent demonstration by flame photometry that beer is truly low in sodium has stimulated further studies on the use of beer in diet therapy.

Table I lists the sodium content for beer in 25 breweries in the United States, as determined by flame photometry.[1] The twenty-five samples examined disclose an arithmetical average sodium content of 6.95 mg. per 100 Gm., with a low of 1.52 and a high of 20.35 mg. The samples represent approximately 37½ per cent of the total United States production capacity.

TABLE I

Comparative Sodium Content of Beer in 25 U. S. Breweries

Beer and ale	Brewery code no.	Beer and ale	Brewery code no.
Mg./100 Gm.		*Mg./100 Gm.*	
1.52	23	7.05	4
1.70	16	8.20	6
2.00	18	9.17	20
2.18	19	9.44	3
2.40	2	10.20	11
2.50	21	10.24	7
2.68	17	10.24	10
2.87	22	13.15	14
2.97	1	13.30	15
4.13	5	14.00	25
4.17	9	14.60	12
4.47	8	20.35	24
6.32	13		

Public drinking water supplies containing less than 10 mg. per 100 cc. are generally accepted[2] as suitable for low sodium diets. This is in excess of the figure just shown for the United States average sodium content of beer of 6.95 mg. per 100 Gm. This is compared in Table II with the sodium value of various beverages usually permitted on the low sodium diet.[2]

TABLE II

Sodium Value of Various Beverages

	Sodium
	Mg./100 Gm.
Ginger ale	8
Whole milk	51
Root Beer	8
Carbonated water	18
Lemon-lime soda	7
Cola drinks	1–15

PLAN OF STUDY

The sodium content of beer is standard by chemical assay from bottle to bottle, but there is wide variation in the sodium content of many foods used in the "low salt diet." We decided to test the effect of beer in the low salt diet on normal patients, that is, patients without heart or kidney disease, to see if true salt restriction could be obtained. Since the body tends to conserve sodium when the sodium intake is limited, a suitable method of determining whether true salt restriction is being obtained is to measure the 24-hour output of urinary sodium while the patient is on a restricted sodium intake. If true sodium re-

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striction is achieved, the urinary level of sodium excretion should fall rapidly to a low level and remain at a low level as long as salt restriction is maintained.

Methods

Four patients with no evidence of cardiac or renal disease were placed on a 500- or 250-mg. regular hospital "low sodium" diet for a period of five days. The fluid intake was limited to 2000 cc. per day. The daily urinary excretion of sodium was measured. During the second five-day period, one-fourth of the total calories in the low sodium diet were obtained in the form of a standard American beer (2.9 mg. of sodium per 100 Gm.) This is equivalent to 1530 cc. of beer per day. The total fluid intake was similarly maintained at 2000 cc. per day, and again the daily urinary excretion of sodium was measured. After five days on this program, the patients were again returned to the regular 500- or 250-mg. sodium hospital diet, and similar measurements were made as during the first period.

Table III shows the type of diet used in this project. It will be seen that beer may be substituted in the diet without diminution in protein content. The beer used in this project had the following mineral constituents per 12-ounce bottle:

Phosphorus	125.80 mg.
Calcium Oxide	28.56 mg.
Iron	0.08 mg.
Copper	0.07 mg.
Manganese	0.03 mg.

The nutritional breakdown of the regular hospital 250- and 500-mg. sodium diet compared with the diet containing beer is listed in Table III. It will be seen that the inclusion of beer in the low sodium diet brings the calcium, phosphorus, and iron content over the minimum recommendations of the National Research Council (Table IV).

Beer may also be a valuable part of such a diet because of its vitamin content, particularly riboflavin, pyridoxine, and niacin. Beer has a relatively low caloric content of approximately 160 cal. per 12-oz. bottle.

TABLE III

Type of Diet Used in Project

Type of diet	Diet before addition of beer	1150 and 1530 cc. beer alone	Total for diet including beer
Calories	1177–1262	480–640	1650–1900
Protein, Gm.	60–68	3.20–4.30	62–72
Carbohydrate, Gm.	117–124	50–67	167–191
Fat, Gm.	49–63	—	49–63
Alcohol, Gm.	—	40–55	40–55
Fluid, cc.	470–850	1150–1530	2000
Sodium, mg.	220–470	34–45	254–515

TABLE IV

Mineral Breakdown of Regular Low Salt Diet and Low Salt Diet with Beer Included

	Calcium	Phosphorus	Iron
	Gm.	*Gm.*	*mg.*
NRC recommended allowance per day	1.0	1.5	12
Diet including beer	1.75	1.77	13.14
Regular hospital 500 mg. Na diet with milk	0.9	1.4	13.9

Reference to Figure 1 shows that during the first five-day period these patients had a rapid fall in the urinary excretion of sodium. This low total daily excretion of sodium continued

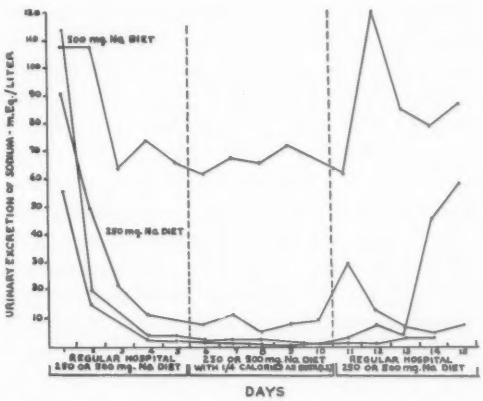

Fig. 1. Daily output of sodium of 4 patients while on the regular hospital low salt diet and the low salt diet with the inclusion of beer. Note low sodium excretion during period of beer included diet. Note irregular and elevated excretion of urinary sodium during last period when patients were again placed on the regular hospital low salt diet, indicating that rigid sodium restriction was not being obtained.

throughout the period in which beer was included in the diet. However, it will be noted that during the last five days when the patients were again placed on the regular hospital low sodium diet there was wide fluctuation in the urinary output of sodium in three cases, indicating that true sodium restriction was not being maintained as well during this period as during the period when the diet included beer. The reason for this is probably that the regular hospital low sodium diet varied considerably in actual sodium content from day to day, due to the variation in the sodium content of the foods used. However, the inclusion of one-quarter of the calories in the form of beer with accurate sodium content from bottle to bottle made possible a more consistent and lower intake of sodium from day to day as indicated by the low and even excretion of sodium in the urine.

Discussion

A search of the modern scientific literature reveals that little attention has been given to the use of beer in therapeutic situations. Some reference has been given to the nutritive value of beer, and other information regarding its nutritional value can be inferred from studies performed on alcohol and alcohol solutions. Daniel[3] concludes from his study of alcohol metabolism and his review of the literature that alcohol spares carbohydrate, fat, and protein because of the fact that it cannot be stored in the body. It is rapidly oxidized in the presence of normal liver function to acetaldehyde and then to acetic acid and acetates. These can be oxidized by all the tissues of the body, providing energy for muscular work and for the maintenance of body temperature. Daniel concludes that as much as 70 per cent of the caloric value of ingested alcohol can be thus utilized.

Newman, Wilson, and Newman[4] have concluded that the ability of the average individual to metabolize alcohol per 24-hour period far exceeds the amount contained in 36 to 48 ounces of beer.

Some attention has been given to the effect of beer and of solutions of ethyl alcohol on renal function. Bruger, Localio, and Guthrie[5] report their observations on the renal function of various patients to whom alcohol itself was administered. They observed that moderate diuresis was frequently induced, even in patients with marked impairment of renal function. No untoward effects in subjects with normal kidneys were observed, nor were they observed in patients suffering from various stages of glomerulonephritis. A transient rise in the red cell component of the Addis count was observed in patients with "arteriosclerotic nephritis" (nephrosclerosis), and in these patients impairment of renal function studies increased temporarily following the ingestion of alcohol. They were able to state categorically, however, that the ingestion of alcohol (in amounts somewhat greater than would be contained in 36 to 48 ounces of beer) did not produce aggravation of chronic diffuse glomerulonephritis, nor did it retard the expected degree of recovery.

Strouse *et al.*[6] have shown that there are no harmful effects from the use of beer in the diabetic diet.

Summary

The true low sodium content of beer is indicated. Analysis of 25 representative samples of beer reveals an average sodium content of 6.95 mg./100 Gm. This may be compared to drinking water containing 10 mg./100 cc. used in the "low salt" diet.

The study of the urinary excretion of sodium in four patients while on a regular low sodium diet and while on a low sodium diet including beer indicates that more accurate salt restriction is obtained on the diet in which beer is included.

The use of beer in some therapeutic situations is discussed.

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Resumen

Valor nutritivo de la cerveza, con referencia a la dieta pobre en sodio

Se demuestra el contenido verdaderamente bajo en sodio de la cerveza. El análisis de 25 cervezas representivas revela un contenido de sodio de 6,95 miligramos/100 gramos. Esto se puede comparar con el agua, que contiene 10 mg./100 cc., y que se emplea comunmente en la dieta pobre en sodio.

El estudio de la excreción de sodio en las orinas de 4 pacientes durante su adherencia a una dieta pobre en sodio *standard* y luego a una dieta pobre en sodio pero incluyendo la cerveza, indica que una restricción más precisa de sodio se obtiene con la dieta en la cual está incluida la cerveza.

Se discute el uso la cerveza en varias situaciones terapéuticas.

The "Serial Why"

"In thinking about the fundamental nature of any phenomenon, the human mind invariably tends to analyze it from two essentially distinct viewpoints. We want to know its *primary cause* and its *primary constituent element*. . . .

"This innate quest for the Primary is also quite evident during the period of mental awakening in every child. It manifests itself by what might be called the 'serial why,' which leads to the following type of conversational pattern: 'Why is it dark at night?' 'Because the sun sets.' 'Why does the sun set?' 'Because the earth turns away from it,' and so forth, until the hard-pressed adult succeeds in changing the topic.

"Our craving to climb up along such question-ladders does not diminish with maturity; only our hopes of reaching the top rung fade away with age, for we come to realize that it is just as inherent in human nature to be blind for the Primary as it is to look for it. Yet, as soon as man understands that, for him, the ladder of comprehension has no end, he can find comfort in the realization that, consequently, there also is no limit to his possible progress; no matter how advanced his wisdom, he always remains capable of yet another step forward."

—Hans Selye. *Texas Reports on Biology and Medicine* 12: 396–397, 1954.

Finding the Mean in Medicine

"After centuries of wavering between religion and philosophy, magic and mysticism, dogmatism and rationalism, medicine returned again to reliance upon facts proved by experience, to the truths that can be confirmed by objective scientific evidence. For a time it looked as if the laboratory was to become the centre of medical activity at the expense of the clinic, but saner counsels prevailed, and a reaction against undue materialism has brought us back today to something very close to the Hippocratic ideal—studying at the bedside of the patient those factors which can best be observed there, but doing so in the light of that wider knowledge and deeper understanding which has been the invaluable contribution of the basic sciences to medicine. However potent, however marvellous may be the weapons which science can forge in her laboratory to arm the physician in his fight against disease, they must never be allowed to take him away from his post of honour beside the sickbed, for it is there that the medical man will achieve his ultimate triumph, the cure of his patient."

—A. D. Trendall. *The Medical Journal of Australia* 41 (4): 120, 1954.

Effects of Choline on Cardiovascular Lesions Induced by Feeding Large Doses of Vitamin D

By GEORGE F. BUCKLEY, M.D., AND W. STANLEY HARTROFT, M.D., PH.D.*

TWENTY-SIX years ago, Kreitmair and Mall[1] reported the production of vascular calcification in rats fed high doses of activated ergosterol, an observation that has since been confirmed repeatedly. Duguid[2] gave detailed descriptions of this type of aortic sclerosis; Ham and Lewis[3] provided excellent illustrations of the intimal sclerosis that rapidly develops in the coronary arteries of rats given massive single doses of vitamin D. These reports and others have been the subject of several reviews.[4] In nearly all the experiments that have been reported, investigators employed commercially available rations for the basal diet. It has previously been reported from this laboratory that a significant number of young rats fed diets high in fat but low in choline regularly developed vascular lesions which were absent in pair-fed controls fed the same diet supplemented with choline.[5-8] The gross appearance of the aortas in many of the choline-deficient rats resembled that of sclerotic aortas in rats subjected to hypervitaminosis D. Therefore, it was decided to determine whether or not dietary lipotropic supplements would alter significantly the incidence of cardiovascular lesions induced by excessive intakes of Vitamin D in rats fed a food mixture low in choline. In essence, our findings showed that lesions were absent in the coronary arteries of nearly all the animals receiving a dietary supplement of 0.85 per cent choline chloride in addition to 15,000 to 20,000 units of vitamin D daily, and all their aortas were normal. Lesions at comparable sites developed in 50 to 80 per cent of rats similarly treated but not provided with the lipotropic supplement.

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METHODS

One-hundred and sixteen Wistar rats (males; 120–150 Gm.) in four groups were used in the experiment. Twenty-five animals (Groups 1 and 7; Table I) were fed the basal low choline diet *ad libitum*. Twenty-five additional rats (Groups 2 and 8; Table I) were offered and consumed daily similar amounts of the basal diet supplemented with 0.85 per cent choline chloride. Thirty-three animals (Groups 3, 5, and 9; Table I) were pair-fed the basal diet supplemented with enough calciferol in corn oil so that each ingested daily 15,000 to 20,000 units of vitamin D. Animals in groups 4, 6, and 10 (Table I) received supplements of both choline and calciferol. The per cent composition of the basal diets was as follows: casein 10, alcohol-extracted peanut meal 30, alpha soya protein 5, LP* salts 3, PDW* vitamins 1, cellu® flour 5, sucrose 10.5, lard 35.0 alpha tocopherol acetate 0.010, cod liver oil concentrate 0.015, cinnamon 0.03. Calciferol was dissolved in corn oil so that 1 ml. contained 10,000 international units of vitamin D. The mixture was added at the level of 20 per cent to the

* The ingredients of the salt mixture and the vitamin mixture have been published previously.[9]

TABLE I

Group No.	No. of rats	Dietary choline chloride (0.85 per cent)	Dietary calciferol (15,000–20,000 I.U./day)	No. of days on diet	No. of rats with cardiac muscle lesions	No. of rats with coronary arterial sclerosis	No. of rats with aortic sclerosis
1	10	0	0	35	2	2	1
2	10	+	0	31	0	0	0
3	10	0	+	35	6	8	8
4	10	+	+	31	1	2	0
5	8	0	+	35	4	5	4
6	8	+	+	31	0	0	0
7	15	0	0	42	9	8	8
8	15	+	0	41	0	0	0
9	15	0	+	38	8	9	7
10	15	+	+	41	1	3	0

basal diet at the expense of the lard. The cinnamon, which was added to all diets, served to stimulate the animals' appetites. Details of the methods of housing the cages, preparation of diets, etc., have been published previously.[9]

The experiment was carried out in three stages. In the first, 40 animals were used (Table I) in four groups (Nos. 1–4) of ten animals each. In the second stage, there were only two groups (Nos. 5 and 6) of eight rats in each; both received calciferol in their diets, but only one group (No. 6) was given the choline supplement (Table I). In the third stage of the experiment (Table I), again four groups (15 rats in each) were employed (Nos. 7, 8, 9, and 10). The various supplements fed to each group are indicated in the table. In the first two stages of the experiment the deficient animals were maintained for an average period of 35 days before sacrifice, and the choline-supplemented groups for 31 days. The discrepancy of four days developed because the groups were started at different times. In the third stage this time difference was avoided, and actually the choline-supplemented animals were observed for a slightly longer period than the deficient ones.

Animals were sacrificed under ether-inhalation anesthesia, and blocks of tissue from heart, aorta, liver, kidney, spleen, and pancreas were fixed by immersion in formol-calcium solution. Frozen sections were cut routinely of all hearts and aortas and stained by Wilson's modification of Lilly's supersaturated Isopropynol Oil Red O Technique.[10] In addition, a variety of special strains were carried out on these and other tissues (see below).

Results

The number of rats exhibiting lesions in heart muscle, coronary arteries, and aortas in the various groups are given in the table. In hearts and aortas of members of the basal choline-deficient groups (Nos. 1 and 7), lesions induced by choline deficiency *per se* developed in 25 to 60 per cent of the rats. The gross and microscopic appearances of this type of vascular injury have been described previously in reports from this laboratory.[5,6] Choline supplements to the basal diets (without added calciferol) completely prevented lesions in the organs and vessels of control rats in both stages of the experiment (Groups Nos. 2 and 8). Addition of calciferol to the basal diet (Groups 3, 5, and 9) more than doubled the incidence of cardiovascular lesions (50 to 90 per cent) in 35 rats fed this ration. Aortas of all 33 control rats (Groups 4, 6, and 10) fed the basal diet supplemented with *both* choline and calciferol, were normal, and only minimal lesions were found in coronary arteries of five (15 per cent).

Not shown in the table are the effects on the kidneys of rats on the various dietary regimens. In almost every animal that did not receive the dietary supplement of choline chloride, the kidneys were moderately or severely damaged, particularly in those rats that had ingested calciferol. But neither

gross nor microscopic evidence of renal damage could be found in any of the animals given the choline-supplemented diet with or without added calciferol. The type of renal injury induced by the low choline diets conformed to the descriptions previously published by Christensen[11] and by one of us.[12] The addition of calciferol to low choline diets intensified these lesions and increased the amount of calcium salt deposition in necrotic tubules.

The Aortic Lesions

The gross and microscopic appearances of the aortic lesions in the choline-deficient rats were not appreciably altered in those animals that also received added vitamin D (Figs. 1 and 2). In the advanced stages of the lesion the intima was frequently thickened and the lumen narrowed by plaques composed of hyperplastic endothelial cells. In the cytoplasm of these cells small droplets of stainable fat were frequently present. The underlying media appeared necrotic, calcified, and in some instances hyperplastic. In the example illustrated in Figure 1, a fracture of a calcified medial bar is in an early healing stage with callus formation ("collar-button lesion"). It is difficult to discern any consistent differences in the nature of the aortic lesions induced by choline deficiency *per se* and those by calciferol supplements to the low choline diet. Calcification frequently appeared to be as prominent a feature in the one case as in the other. In these experiments, aortic lesions were not produced by high intakes of calciferol unless the choline supplement was omitted from the diet consumed by the animals.

Coronary Arterial Lesions

In their most advanced form, coronary arterial lesions in members of the choline-deficient calciferol-supplemented groups could be readily distinguished from those seen in rats that had received the basal choline-deficient diet alone. Calciferol supplementation of the choline-deficient rations consumed by rats in Groups Nos. 3, 5, and 9 was associated with lesions in the coronary arteries that resembled those observed in the aortas, but on a smaller scale. The intima of the affected vessels was thickened and heaped up; stainable fat could be demonstrated in the proliferated endothelial cells; and hyperplasia and hypertrophy of the underlying media with some necrosis and calcification was frequently observed (Fig. 3).

In the coronary arteries of the choline-deficient animals that did not receive calciferol, lesions were neither as advanced nor as frequently encountered. Abnormalities were confined almost exclusively to simple deposition of stainable fat in intimal endothelial cells, media, and occasionally adventitia of affected vessels (Fig. 4). Aside from some thickening of the intima by hypertrophy of endothelial cells, there were no apparent alterations in the architecture of the arteries, although structural changes have been encountered in rats fed low choline diets for longer periods.[5]

Damage to Cardiac Parenchyma

Abnormalities in the cardiac parenchyma of choline-deficient rats consisted of deposits of stainable fat within the cytoplasm of muscle cells, myocardial necrosis, lysis, and, in some instances, fibrosis. In those choline-deficient animals receiving calciferol supplements, necrotic muscle fibers were sometimes calcified, but otherwise no consistent differences could be detected in the type of lesion encountered in hearts of animals of the various groups. The microscopic appearance of the lesions in animals fed low choline, high fat diets has been reported;[13] the addition of calciferol to similar diets appeared only to increase slightly the incidence of the lesions.

Livers

In all the choline-deficient animals, whether receiving calciferol supplements or not, the livers contained abnormal deposits of stainable fat; choline prevented the accumulation of lipid in the livers of the control rats. Hepatic fibrosis or cirrhosis did not develop in any of the choline-deficient rats, presumably because of the short duration of the experimental period.

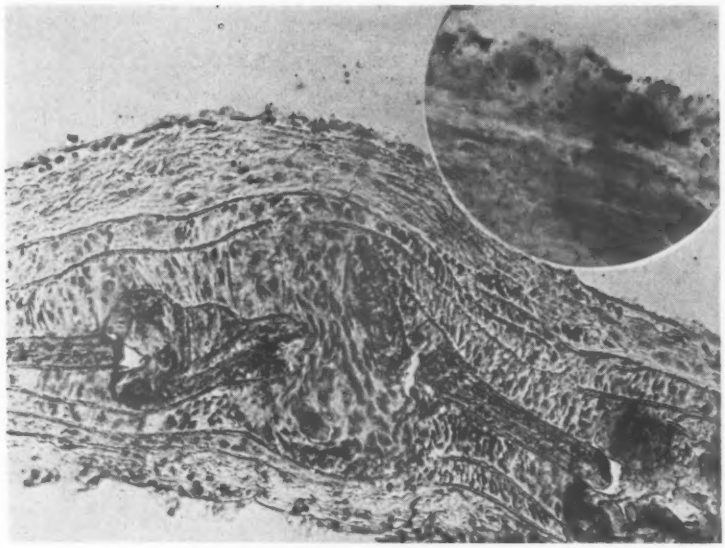

Fig. 1. Advanced aortic sclerosis in a choline-deficient rat (that did not receive added vitamin D). Note the thickened intima and the healing fracture of the underlying calcified media; × 100. The inset demonstrates the presence of stainable fat droplets (black) in the intima; × 800. Frozen section stained with Oil red O.

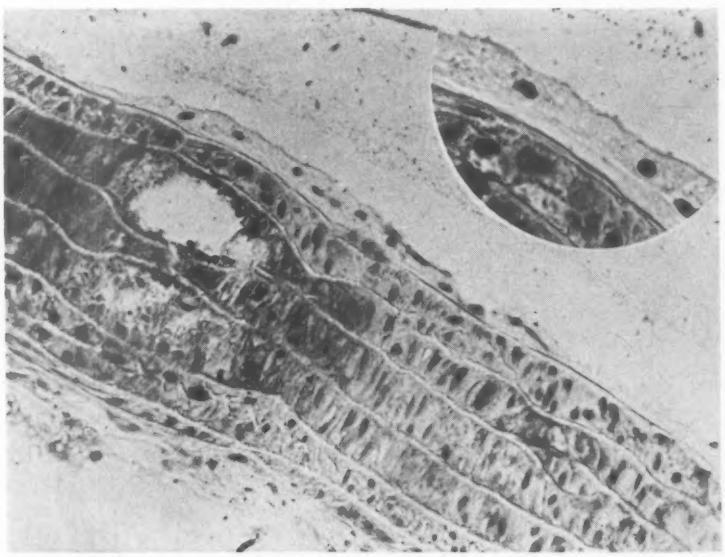

Fig. 2. Stain and magnifications as for Fig. 1. An early stage of aortic sclerosis is seen in this aorta from a choline-deficient rat that received the excessively high supplement of vitamin D. Calcium has dropped out of the hole in the necrotic media which underlies the slightly thickened intima. Little fat is present in the intima (inset). In many rats of this group, the aortic lesions advanced to a stage indistinguishable from that shown in Fig. 1.

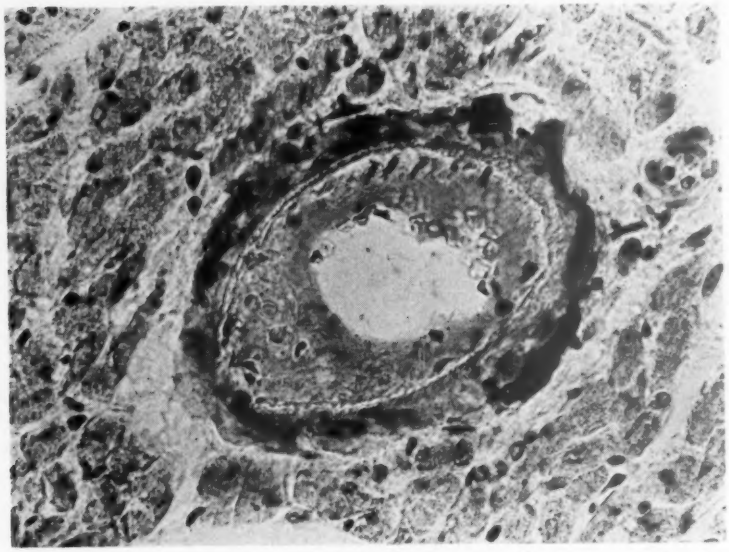

Fig. 3. Coronary artery from a choline-deficient rat that did not receive the supplement of vitamin D. Fat (black) is deposited in media and adventitia. Frozen section stained with Oil red O; × 500.

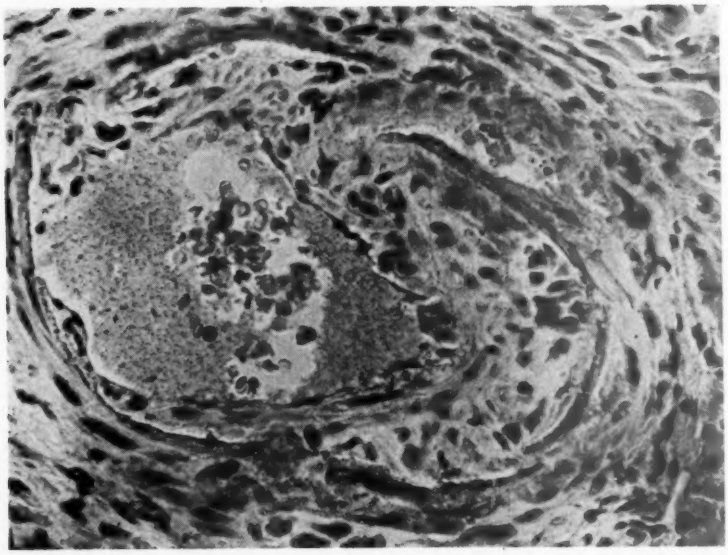

Fig. 4. Stain and magnification as for Fig. 3. The tremendously thickened subintima and media are shown in this coronary artery which is considerably narrowed. Only small amounts of stainable fat are present in the lesion at this stage. The vessel is from a choline-deficient rat that received a high dose of vitamin D.

Discussion

Despite excessively high doses of vitamin D, those animals that also received the dietary supplement of choline chloride (0.85 per cent) were clearly afforded a large measure of protection against the type of cardiovascular damage observed in many of the rats consuming the basal diet containing calciferol without added choline. Calculations based on the food intake of the animals (which averaged 8 to 10 Gm. per day per rat) indicated that rats consuming the calciferol-supplemented diet obtained between 15,000 and 20,000 international units of vitamin D per day. Our data provide no information on the protective effect of a choline supplement under conditions where rats may receive appreciably more than this amount of vitamin D. But it seems likely that with higher doses of the vitamin the protective effect of choline would be lost. It is also possible that the protective effect of choline would not have been demonstrated had the same daily intake of vitamin D used in the present experiment been continued for longer periods.

Comparison of Calciferol-induced and Choline-deficient Cardiovascular Damage

Neither gross nor microscopic differences that could be related to the amount of vitamin D in the diet were detected in the appearance of the aortic lesions. But by their lesions the coronary arteries of choline-deficient rats that were given calciferol could be easily distinguished from arteries of rats that did not receive extra vitamin D. In the coronary arteries of the choline-deficient animals, abnormal deposits of lipid were present with hypertrophy but not hyperplasia of intimal endothelial cells, whereas the lesions in the choline-deficient, calciferol-supplemented rats exhibited more profound structural abnormalities (See Fig. 4). The difference in the lesions, however, may be more apparent than real, because it may only be associated with the stage and severity of the injury. In previously reported experiments,[5] coronary arteries in rats fed low choline diets for four to six months resembled those seen in the calciferol-supplemented rats of the present short-term experiment. The demonstration that choline supplements in the latter afforded a high degree of protection against the vascular damage induced by calciferol in choline-deficient rats, suggests that the nature of the lesions in not only the aortas but also the coronary arteries may be basically similar in both conditions. But we feel at the present time that it is impossible to conclude without further information whether or not the coronary arterial lesions induced by choline deficiency are fundamentally the same as those produced by high doses of vitamin D.

The Protective Effect of Dietary Choline Supplements on Vascular Lesions Induced by Hypervitaminosis D

Previous experiences in this laboratory have never suggested that dietary choline protects against anything but choline deficiency. The data provided by the experiments reported here may constitute an exception to this rule, for which an explanation is not provided by any of the available data. Renal damage in rats consuming calciferol was absent in members of the choline-supplemented groups, but prominent in the choline-deficient animals. It is possible that damaged kidneys were not effective in excreting excessive amounts of calcium in the blood of the choline-deficient, calciferol-supplemented animals, whereas the apparently intact kidneys of choline-supplemented, calciferol-supplemented rats may have accomplished this more effectively. Measurements of the levels of calcium in the serum of the rats of the various groups might have yielded information that would have thrown light on this problem. Further investigations along these lines would be necessary to provide these data.

In previous publications,[6,8] the role of renal damage in the production of vascular lesions in choline-deficient rats has already been considered. It is possible that choline deficiency *per se* induces vascular lesions in rats as a result of initial renal damage. Conclusive evidence concerning this point is not yet available, but the investigations of Lehr and

Churg,[14] Wissler,[15] and Holman[16] indicate that kidney damage induced by a variety of methods in susceptible animals may be regularly associated with lesions of aortas and coronary arteries. If cardiovascular damage in choline-deficient rats should prove to be of renal origin, the prevention of damage to the vessels of calciferol-fed rats by choline supplements may be simply a manifestation of the protective action of choline on the kidney. Whichever mechanism proves to be true, however, there is now considerable evidence to indicate that, directly or indirectly, lipotropic supplements aid in the maintenance of the heart and blood vessels of experimental animals.

The Role of Lipotropic Substances in the Treatment of Arterial Disease in Man

Katz and Stamler[17] have recently reviewed the role of lipotropic factors in the prevention and treatment of both experimental and clinical vascular disease. They quote their previous conclusion:[18] "Neither on theoretical nor experimental nor clinical grounds is there today a firm scientific basis for the widespread clinical use of costly lipotropic preparations in the prophylaxis and/or therapy of human atherosclerosis." This conclusion is based on the apparently negative result of clinical trials of the therapeutic use of lipotropic factors in the treatment of human atherosclerosis, despite initial encouraging reports by Steiner[19] and others. A number of investigators[20,21] have reported that choline supplements failed to protect rabbits against cholesterol-induced atheroma. In these experiments, the basal diets employed already contained adequate amounts of lipotropic factors and their cholesterol content was very high. Under these conditions, the published data clearly indicate that dietary choline does not afford any protection to animals against vascular injury so induced. In our experiments, we have been able to show a protective effect of choline supplements against calciferol-induced injury to vessels only when the basal diet was low in lipotropic factors. Whether or not choline deficiency is ever responsible for directly inducing disease in vessels of man or for facilitating their injury by other agents remains to be demonstrated. We are in agreement with the conclusions of Katz and others that at the present time clinical use of lipotropic factors in human arterial disease is entirely unwarranted. Nevertheless, we believe that the available results do justify further exploration of any relations that may exist between dietary choline deficiency and cardiovascular disease in experimental animals and possibly also in man. Heart disease is high in the list of causes of death in most countries. Every experimental approach that may add to our knowledge of factors responsible for the health of the heart and vessels should be pursued vigorously.

Summary and Conclusions

Nine of 25 rats fed a basal choline-deficient, high fat diet developed varying degrees of aortic sclerosis. Nineteen of 33 choline-deficient rats fed the same basal diet but supplemented with high doses (15,000–20,000 international units per rat per day) of vitamin D (calciferol) developed essentially the same type of aortic lesions. Choline supplements added to the basal diet completely prevented the development of aortic sclerosis in 25 rats and was also successful in preventing lesions in an additional 33 animals fed the basal diet supplemented with large amounts of vitamin D. A similar but not completely protective effect of the choline supplement on their coronary arteries was demonstrated.

Choline supplements in the basal diets (with or without added calciferol) consumed by the rats prevented the development of renal damage.

The mechanism of the protective action of choline supplements on the cardiovascular system of rats given excessive amounts of vitamin D and the possible role of the kidney in this regard is discussed.

Clinical applications of these findings to either the prevention or treatment of arterial disease in man are not apparent at the present time. However, in view of the data presented, it would seem that therapeutic use

of large doses of vitamin D, for example, in the treatment of scleroderma or arthritis, should be accompanied by administration of abundant amounts of lipotropic factors.

ACKNOWLEDGMENTS

Professor C. H. Best of the Banting and Best Department of Medical Research, University of Toronto, provided valuable direction and aid throughout the course of these investigations. The authors gratefully acknowledge the generous co-operation of Dr. Jessie H. Ridout, research associate, Banting and Best Department of Medical Research, University of Toronto, for her assistance in the preparation of diets for the feeding of animals.

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Resumen

Efectos de la colina sobre las lesiones cardiovasculares inducidas por la suministración de grandes dosis de vitamina D

De 25 ratas alimentadas con una dieta basal deficiente en colina, 9 mostraron varios grados de esclerosis aórtica. Diez y nueve de 33 ratas deficientes en colina alimentadas con la misma dieta basal pero suplementada con grandes dosis (15.000–20.000 u.i./rata/día) de vitamina D (calciferolo) mostraron lesiones aórticas esencialmente del mismo tipo. La adición a la dieta basal de suplementos de colina impidió completamente el desarrollo de

la esclerosis aórtica en 25 ratas y logró también prevenir la aparición de lesiones en otros 33 animales alimentados con la dieta basal suplementada con grandes cantidades de vitamina D. El suplemento de colina tuvo un efecto similar, pero no completamente protectivo, sobre las arterias coronarias.

La suplementación con colina de las dietas basales (con o sin adición de calciferolo) ingeridas por las ratas impidió el desarrollo del daño renal.

Se discuten el mecanismo de la acción protectiva de los suplementos de colina sobre el sistema cardiovascular de ratas que han recibido cantidades excesivas de vitamina D y el posible papel del riñon en este respecto.

Las aplicaciones clínicas de estos hallazgos, sea a la profilaxis sea al tratamiento de las enfermedades arteriales en el hombre, no son aparentes en la actualidad. Sin embargo, a la luz de los hechos presentados, pareciera que el uso terapéutico de grandes dosis de vitamina D—en el tratamiento de la escleroderma o de la artritis, por ejemplo—debiese acompañarse de la administración de cantidades abundantes de los factores lipótropas.

Nitrogen Balance *as Related to* Caloric and Protein Intake *in* Active Young Men

By Doris Howes Calloway, ph.d.,* and Harry Spector, ph.d.†

The physiologic effects of restricted feeding, particularly on protein utilization, have occupied the interest of nutritionists since the time of Voit and Rubner.[19] Impetus for experimental investigation of the problem has been lent, historically, by periods of war and catastrophe when national food supplies are critical. In recent years, this problem has warranted the particular attention of nutritionists in the Department of Defense because of the recognition of situations of limited feeding capabilities created by modern mobile warfare. In this category fall troops cut off from normal supply channels, especially victims of air and sea disaster, and civilian populations of disrupted areas. Under military support, many data have been gathered which have not been widely available to scientists and have not been consolidated with other clinical and laboratory findings. As an aid in the design of a multipurpose survival ration, the information relative to normal active men in the military age group has been compiled, emphasis being placed on the more acute, short-term experiments.

The information on nitrogen balance in chronic inanition has already been critically reviewed by the Minnesota group,[18] and that relating to protein-depleted man by Benditt and co-workers.[2]

From the Quartermaster Food and Container Institute for the Armed Forces, Chicago, Ill.

This paper reports research undertaken at the Quartermaster Food and Container Institute for the Armed Forces and has been assigned number 462 in the series of papers approved for publication. The views or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the views or indorsement of the Department of Defense.

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Selection of Data

Studies were chosen from the literature in which the subjects were young men, essentially normal in weight and nutritional status, who were permitted at least sedentary activity. Data on control groups indicate that the men normally maintained body weight at intakes of 3000 to 3600 calories per day. Estimates of caloric expenditure during the restriction phase ranged between 2000 and 3500 calories daily. Only two representative reports in the area of adequate caloric intake were chosen from the wealth of material available,[5, 11] one at a low protein level, and a second where the protein allowance was liberal. Included are military field trials and laboratory studies of military personnel, college students, Civilian Public Service Camp workers, and conscientious objectors.

It has been recognized that continued dietary restriction ultimately results in adaptation to a lowered intake of protein[12] or of calories.[18] However, in the caloric intake range 1500 and above, some long-term studies were drawn upon because of the dearth of other information; where these investigations had to be included, only the data from the first two weeks were used.

Many reports were excluded from this survey because of inadequate quantification of dietary intakes, questionable values for excretion, or simply because insufficient data were provided. Also excluded from consideration were experimental findings in frankly obese individuals, in men at bed rest, and in those fed parenterally.

If feces were not analyzed for nitrogen content, arbitrary allowances were made. Where

TABLE I
Nitrogen Balance in Protein-free Feeding

Caloric intake		Nitrogen balance			
Range*	Composite mean	Range*	Composite mean	Number of observations	References
Cal./day	*Cal./day*	*Gm./day*	*Gm./day*		
0	0	−7.9 to −13.0	−12.0	87	3†, 4, 6, 7, 14, 22, 27, 39, 40
31–200	119	−9.1 to −11.1	−10.9	17	6, 8, 40
400–500	441	−6.6 to −9.4	−8.4	22	6, 13, 17, 22, 40
669–787	728	−7.0 to −7.4	−7.2	10	33, 34
800–958	891	−6.3 to −7.8	−7.2	34	6, 24, 25, 29, 30, 32, 35
—	1200	—	−7.3	2	6
—	1443	—	−6.3	5	36
—	2400	—	−7.4	1	38
—	2800	—	−6.8	8	7

* Range of experimental means.
† Including literature reviewed.

protein-free diets or protein-containing diets of less than 1000 calories per day were fed, one gram of nitrogen—the average value of fecal analyses reported—was added to the excretion. When protein was fed and the caloric intake was above 1000, the correction figure of 1.28 grams was used, as suggested by Reifenstein, *et al.*[26]

A composite mean for all the experiments within a st..ted range of caloric and protein intake was derived by weighting the mean of each experimental group for the number of subjects observed. As the majority of reports did not include data on daily nitrogen excretions, the composite means were derived from the average values for the periods of restriction tested. Although nitrogen excretions during the first two days of the experimental period reflect primarily the influence of preceding protein intake, the mass effect during an average restriction period of ten days was not significantly altered by the inclusion of this early period, inasmuch as the preceding equilibration diet in all cases furnished a normal intake of protein. Examination of individual studies shows wide variation among subjects and between means of related experiments. The summations should be viewed in this light.

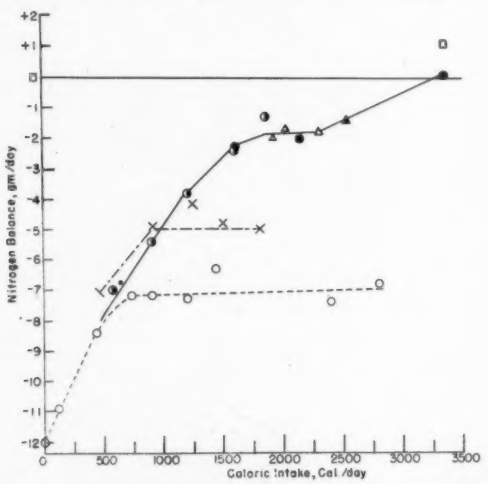

Fig. 1. Nitrogen balance at various levels of caloric intake.

○ Protein-free followed by Nitrogen intake, Gm./day: ↘ 1.0–1.9, × 2.4–5.0, ◑ 5.4–7.7, ● 8.1–9.7, △ 10.4–11.7, ▲ 12.4, □ 15.4.

Interrelationships of Protein and Caloric Limitation

To establish a baseline for determination of nitrogen utilization, consideration must first be given to the excretion of nitrogen when none is fed. These data are presented in Table I and are shown graphically in Figure 1. Nitrogen losses amounted to 12 grams daily in fasting, and the protein deficit was maximally reduced by supplying approximately 700 protein-free calories. Increasing the caloric intake to 2800 was without further advantage in the sparing

TABLE II

Nitrogen Balance at Varying Caloric and Nitrogen Intakes

Caloric intake		Nitrogen intake		Nitrogen balance		Number of observations	References
Range*	Composite mean	Range*	Composite mean	Range*	Composite mean		
Cal./day	*Cal./day*	*Gm./day*	*Gm./day*	*Gm./day*	*Gm./day*		
400–500	467	1.0–1.9	1.6	−6.5 to −8.2	−7.1	6	17
—	572	—	6.9	—	−7.0	2	6
803–1100	911	2.4–4.5	3.1	−3.2 to −7.4	−4.9	60	14, 20, 29, 30, 31, 32
754–1023	891	5.4–7.7	6.3	−1.6 to −7.9	−5.4	50	24, 25, 27, 30, 32, 33, 34, 35
1200–1331	1256	3.0–5.0	4.5	−1.1 to −6.8	−4.1	25	13, 30, 31
—	1200	—	6.0	—	−3.8	4	30
—	1500	—	3.0	—	−4.8	4	30
1432–1638	1587	6.0–7.6	7.2	−2.0 to −4.5	−2.4	15	5, 18, 30
1522–1650	1596	8.1–9.7	8.9	+0.2 to −4.8	−2.3	36	5, 16, 20, 36
—	1800	—	3.0	—	−5.0	4	30
1800–1948	1854	6.0–7.4	6.6	−0.3 to −3.8	−1.3	33	20, 27, 30, 31, 32
1919–1962	1924	10.4–11.7	11.5	−1.4 to −2.1	−2.0	48	5, 21
2140–2146	2143	8.1–8.2	8.2	−1.8 to −2.1	−2.0	6	14, 27
2028–2135	2030	10.8–11.6	11.5	−1.7 to −2.1	−1.7	49	5, 21
2268–2330	2299	11.1–11.4	11.2	−1.6 to −2.0	−1.8	12	5
2521–2532	2526	—	12.4	−1.3 to −1.5	−1.4	86	21
—	3355	—	8.5	—	+0.1	8	11
—	3342	—	15.4	—	+1.1	12	5

* Range of experimental means.

of body protein, the negativity of nitrogen balance remaining approximately 7 grams throughout.

From Table II and Figure 1 it is apparent that feeding nitrogen to the highest level tested, 6.9 grams daily, was of little benefit when only 400 to 600 calories were supplied. The mean daily negative balance of 7.0 grams of nitrogen falls well within the range of means obtained when no protein was fed. It is apparent that protein fed under these circumstances is largely burned as an energy source, producing a concomitant rise in urinary nitrogen excretion.

An intake of approximately 900 calories was the lowest level at which the addition of protein to the diet produced noticeably less negative nitrogen balance than the same number of protein-free calories. At this calorie level the same reduction in negativity of nitrogen balance occurred with 3 grams as with 6 grams of nitrogen fed. When dietary nitrogen was limited to 3 grams per day, maximum nitrogen retention was attained at approximately 900 calories, and increasing the caloric intake to 1800 did not further reduce the 5 grams of negative balance.

Increasing the energy value of the diet from 900 to 1600 calories when 6 grams or more of nitrogen were fed resulted in improved nitrogen retention. A plateau at 1.8–2.4 grams of negative nitrogen balance was reached at approximately 1600 calories, which persisted through approximately 2300 calories. The plateauing trend over a wide range of both nitrogen and caloric intakes suggests that in this range of 50 to 75 per cent of normal caloric requirement, adjustment of energy expenditure to intake may have taken place so that a relatively constant fraction of actual requirement was met.

On the basis of the 7 grams of total nitrogen excretion which was the baseline for protein-free feeding, it is logical to assume that no increase in the energy content of the diet could promote nitrogen balance when the nitrogen intake is below this amount. The lowest nitrogen intake tested at adequate caloric intake in subjects defined here was 8.5 grams of nitrogen daily; at this intake, nitrogen equilibrium was obtained. At nitrogen intakes of 11 to 12 grams daily, calories were limiting through 2500. These data are in good agreement with the critical value for protein utilization of 1500 calories/M^2 surface area/day derived for protein-depleted men by Benditt and coworkers,[2] and the 35–40 calories/Kg. established in severely undernourished subjects by Beattie *et al.*[1] Beyond this range, these authors state, the nitrogen intake determines the sign and magnitude of nitrogen balance.

The effect of caloric intake on nitrogen balance may then be described by Figure 1, in which the slope of the line is determined by caloric limitation with plateaus related to nitrogen deficit.

In Figure 2, the data are graphed to show the effect of variation in nitrogen intake on nitrogen balance. It is apparent, as previously discussed, that at calorie levels of 400–600, dietary nitrogen is without appreciable benefit. When the caloric intake is approximately 1000, 3 grams of nitrogen may be used to good advantage, but further increase is without benefit. At calorie levels of 1400–2300, 7–9 grams of nitrogen result in essentially the same sparing of body protein as intakes to 12 grams. Between 2300 and 3300 calories, data are insufficient to permit analysis, but the slope of the line indicates that equilibrium might be attained at the 2000–2500 calorie level if the

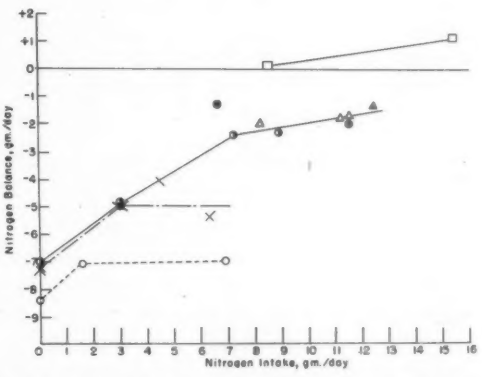

Fig. 2. Nitrogen balance at various levels of nitrogen intake.

Calorie intake cal./day: ○ 400–575, × 750–1100, ◝1200–1350, ◑ 1400–1650, ● 1800–1975, △ 2025–2350, ▲ 2530, □ 3350.

nitrogen intake were increased to approximately 24 grams. Sargent and Johnson[28] in a preliminary oral report of recent studies stated that positive nitrogen balance was approached in a subject fed 2000 calories and 24 grams of nitrogen.

When the full caloric requirement was met, 8.5 grams of nitrogen were sufficient to promote balance, and increasing the intake to 15.4 grams resulted in retention of only an additional gram of nitrogen. Cuthbertson and Munro[9] have reported that the addition of 780 calories to a diet adequate for maintenance reduced urinary nitrogen excretion by 2 grams. A luxus consumption, then, of either protein or calories resulted in more positive nitrogen balance, just as an inadequate intake of either produced a negative balance.

To the general principles set forth—that on a fixed adequate protein intake, energy level is the deciding factor in nitrogen balance and that with a fixed adequate caloric intake, protein level is the determinant—may be added a corollary. That is, at each fixed inadequate protein intake there is an individual limiting energy level beyond which increasing calories without protein or protein without calories is without benefit. Why 600–800 dietary calories should maximally reduce the destruction of body protein but not permit the utilization of dietary protein, or why 3 grams of dietary nitrogen should be most efficiently used at 1000 calories, or 6 grams at 1600, are intriguing questions for which there are no ready answers.

Application

The findings reviewed here provide a basis for the development of a protein-containing military survival ration and the conclusions apply equally to short-term civilian emergency feeding. However, the most critical situation to be considered is that in which water supply is curtailed and the weight or space available for emergency food highly restricted, as in survival at sea or in the desert. Under these conditions provision of about 100 grams of carbohydrate, as suggested by Gamble,[15] is physiologically most desirable. It was shown that the benefits to be derived are several:

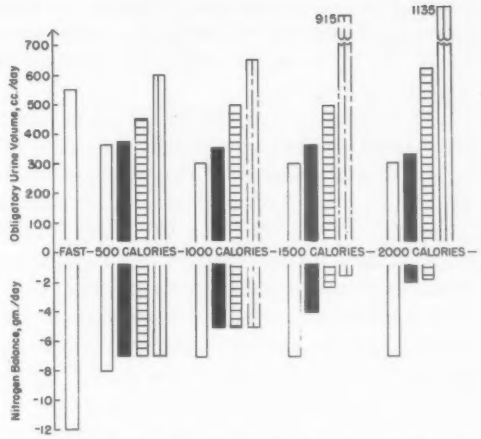

Fig. 3. Calculated alteration in obligatory urine volume compared with nitrogen deficit at varying intakes of protein and calories.

Protein	% of cal.	Gm./500 cal.
□	0	0
■	7.5	9–10
⊟	15	18–20
◫	30	36–40

prevention of ketosis, conservation of body fluid and protein with extension of survival expectancy beyond that of fasting, and a large contribution to morale. Inclusion of protein in such a restricted ration is contraindicated from the standpoint of water balance. The two effects of increasing dietary protein when energy levels are inadequate are demonstrated in Figure 3: a small decrease in nitrogen deficit accomplished at the cost of increasing urinary nitrogen excretion and obligatory urine volume. Assuming maximum renal concentration, the excretion of one gram of urea nitrogen requires 40 to 60 cc. of water.[37] The inclusion, then, of 6 grams of dietary nitrogen in a 500-calorie diet increases the volume required for renal excretion by 250 cc. per day—50 cc. more than fasting requirements.

The relationships between protein and caloric intake seen in Figures 1 and 2 suggest the formulation of a versatile food unit of 500 calories, 7 to 8 per cent of which are derived from protein. Such a unit could then be consumed in any multiple number with maximum benefit from the protein at each energy level. The efficacy of this scheme is illustrated in

Figure 3; it is apparent that increasing the protein intake beyond the suggested unit level results in little or no additional sparing of body tissue protein.

The composition of the diet is apparently not critical. Schwimmer[32] reported that a 30 per cent fat diet was more effective in promoting nitrogen utilization than one containing 10 per cent. The results of the many studies included here do not support this conclusion. Munro,[23] in an exhaustive review of the literature, concluded that there is essentially no difference between carbohydrate and fat in this regard. Sufficient carbohydrate should be provided to prevent ketosis and the amount of fat determined by considerations of caloric density and palatability. The diet should be of uniform composition to achieve maximum benefit of the protein fed in view of the time factor in utilization.[10]

The unit system offers distinct advantage over a set ration allowance in that it may be readily adjusted in consideration of: (1) the level of energy expenditure, (2) the number of people to be fed from the supply available, and (3) the length of time before resupply may be effected.

Summary

Based on an intensive review of published observations on protein intake in the presence of a reduced caloric intake, certain conclusions seem clear.

For young, essentially normal active men, when no protein is fed the protein deficit (negative nitrogen balance) can be maximally reduced by supplying about 700 nonprotein calories. No significant protein-sparing is achieved by intake as high as 2800 calories in the absence of protein. When the caloric intake is approximately 1000, 3 Gm. of nitrogen will produce as much protein sparing as higher quantities of nitrogen. When full caloric requirement is met, 8.5 Gm. of nitrogen promotes balance and little additional storage results even from much larger protein intakes.

These findings, plus others cited from the literature, suggest that a versatile food unit of 500 calories (7 to 8 per cent of which are derived from protein) would be most practical and physiological in the development of a military survival ration, or a short-term civilian emergency feeding.

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Resumen

El equilibrio nitrogenado en relación con el consumo calórico y proteico en jóvenes activos

Parece que ciertas conclusiones bastante

claras puedan deducirse de una revista intensiva de las observaciones publicadas sobre el consumo proteico en la presencia de un consumo reducido de calorías.

En los hombres jóvenes, activos y esencialmente normales, cuando se les priva de toda proteína, el déficit proteico (equilibrio negativo de nitrógeno) se puede reducir al máximo por la suministración de unas 700 calorías no proteicas. Ningún efecto significativo de ahorro de proteínas se logra por una ingestión de hasta 2800 calorías. Cuando el consumo de calorías se aproxima a 1000, se logra con 3 gramos de nitrógeno un ahorro de proteínas tan grande como el conseguido con cantidades mayores de nitrógeno. Cuando se cumple el requerimiento total de calorías, el equilibrio se logra con 8,5 gramos de nitrógeno, y no se consigue mucho almacenaje adicional ni con ingestas mucho mayores de proteína.

Estos hallazgos, con otros citados de la literatura, sugieren que una unidad alimenticia versatil de 500 calorías (7 a 8 por 100 de las cuales serían derivadas de la proteína) sería fisiológica y resultaría muy útil en la confección de una ración de sustinencia para los militares o de un alimento para los civiles en períodos de crisis o desastre.

Effect of High Plant Protein Regimens on the Liver of Dogs

By E. Aubertin, M.D.,* J. Rivière, M.D., P. Loiseau, M.D., P. Debot, Pharm.D., and R. Malineau, M.D.

After the oil has been extracted from oleaginous seeds, a by-product remains, the *tourteau*, the nutritional value of which is by no means negligible, due to its high content of nitrogenous substances.

Of these residues, the richest in protein are those of hulled cotton, hulled peanut, soya, and sunflower seed, in which the protein content is about 50 Gm. per 100 Gm. of the dry weight. The residues of sesame, rape, Nigerian poppy, and flax have a lower protein content.

A great many studies, which are analyzed in the reports of Jacquot [1-2] and Macheboeuf and Tayeau,[3] have been undertaken to determine the amounts of the various amino acids, and especially of the essential amino acids, contained in these residues. Other work was done on these residues to establish their coefficient of absorption (particularly as studied by the balance method) and their assimilative value, as estimated by their effect on growth and by the weight method. These studies have been carried out largely in the rat, but also in other laboratory animals or (with a view to the utilization of these by-products in animal feeding) in cattle, sheep, swine, and poultry.

In 1930, Ribadeau-Dumas recommended the use of sunflower seed meal in the diet of children, because of its high protein content and its digestibility. Later, soya and sunflower seeds were used to make nutritional "cocktails" for infants. In the adult, Balland[4] advised the use of peanut bread; Bonzo Rokusho and co-workers[5] peanut cakes; Leclerc[6] peanut porridges and pastries; and Ranke[7] various food supplements made with peanut meal. During the war, pastry-cooks outdid each other in ingenuity in order to carry on their business with the aid of peanut or sunflower seed meal. Finally, Macheboeuf and Tayeau[3] fought famine edema in a mental institution by incorporating peanut meal in the patients' soup.

In 1942, one of us, together with Dangoumeau and Castagnou,[8] demonstrated that the proteins contained in peanut meal are completely absorbed and assimilated by both dog and man. However, when administered in large amounts to dogs and to a pig, peanut meal produced a rapidly fatal generalized degenerative hepatitis without appreciable renal change. On the other hand, introduced into a regimen of normal caloric value, peanut proteins, given in moderate amounts, do not lead to any liver lesion, even if they constitute the only source of protein in the diet, provided, at least, that the diet contains four times as much carbohydrate as protein. If, without changing the caloric value of the regimen, one progressively reduces its carbohydrate content and increases, in parallel fashion, the amount of peanut meal, one produces diffuse and more or less extensive lesions of fatty degenerative hepatitis, localized particularly at the level of the pericentrolobular spaces in the form of bands radiating in many places toward the periphery of the lobules, to the point of forming an inextricable network.

Furthermore, four volunteers received daily 350 Gm. of bread made with wheat flour containing 10, then 15, 20, 30, and finally 40 per cent of peanut meal, which represented daily amounts of 26, 39, 52, 78, and 104 Gm., respectively, of this meal. In addition, two of the subjects received custards made with peanut meal and a creamed peanut meal sandwich for 15 days, so that the daily ration of one subject was 199 Gm., and 169 Gm. for the

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other. These quantities were administered in addition to the habitual dietary regimen. All these subjects tolerated almost without difficulty daily amounts of 30 to 40 Gm. of peanut meal. In two of them, who had formerly had colitis, dyspeptic and intestinal difficulties and migraine headaches, with signs of hepatic insufficiency in one, forced the termination of the experiment after a few days on a daily ration of 50 Gm. In the two other cases, the observations could be continued, but not without producing difficulties which began as soon as the peanut meal content of the diet reached 150 Gm. per day. In short, the tolerance of the human for this substance is limited, the more so when the liver and intestine are already deficient.

While these studies were being carried out in occupied France, the Americans were publishing their first works on experimental nutritional hepatitis, and following Patek, various clinicians recommended the treatment of cirrhosis by high calorie regimens, rich in protein and poor in lipids.

When, after the war, we learned of this new orientation in the dietary treatment of cirrhosis, we did not fail to compare these regimens with those on which we had produced such important degenerative lesions of the liver, and which were, *par excellence*, high protein and low fat regimens.

These same studies had enabled us to establish that, at least for the dog, an essentially carnivorous animal, a regimen composed exclusively of lean meat, administered in the amount of 1.2 Kg. per day, with bone meal, water, and 5 Gm. of salt, leads merely, in a month's time, to signs of mitochondrial clearing which might be considered as symptoms of hepatic overwork, while the same amount of protein furnished by peanut meal produces a significant diffuse steatosis.

But, because cirrhotics frequently suffer from anorexia and cannot absorb the considerable amounts of meat that Patek advises, a good many authors have had recourse to foods rich in nitrogenous substances which make it possible to supply a sufficient amount of protein in a small volume. Among these, peanut and soya meal are particularly featured, especially since Circle,[9] in 1950, concluded that the proteins of soya and milk are very similar, and Sutermeister and Browne in 1939[10] recommended the employment of this meal to replace casein for many purposes.

Under these circumstances, we resumed the study of experimental dietary hepatitis produced by the residues of oleaginous seeds, in order to discover whether certain of these are less hepatotoxic than others; we have particularly studied, in a comparative way, peanut, soya, and sunflower seed residue meals.

Methods

We employed meals made from peanut, soya, and sunflower seed residues which were supplied to us by the *Grande Huilerie Bordelaise*.

These meals were incorporated into soups containing bread and lean horse meat. All these foods were cooked together and run through the grinder. Initially, the soup contained bread, meat, and peanut residue meal. Later, the meat was reduced, then eliminated, so as to furnish almost all of the protein ration as substances of vegetable origin. The amount of carbohydrate was always equal to or less than that of protein. The animals did not eat their soup regularly, and it is not possible to state with precision the caloric value of the foods they actually ingested every day; but the proportion of carbohydrate to protein was always as just described. Fats were administered in insignificant amounts.

To these regimens were added vitamins A, B-complex, C, D, and E, in suitable amounts, as well as 5 Gm. of sodium chloride per day.

Periodically throughout these experiments, we studied and recorded the liver function of our dogs. Each record comprised 25 results. We refer the reader to our report, published in the *Revue Internationale d' Hépatologie*,[11] for details.

The histologic study dealt with the modifications of the mitochondria, the reticulum, and of the lipid and glycogen content.

Results

1. *Dogs Fed on Peanut Residue Meal*

Two dogs (1 and 2) were placed on a regimen comprising approximately 165 Gm. of

protein and 185 Gm. of carbohydrate, furnished by 200 Gm. of bread, 200 Gm. of lean meat, 200 Gm. of peanut meal. To this daily ration were added vitamins and 5 Gm. of sodium chloride. The experiment began on June 9, 1950.

At the end of September 1950, liver function study revealed a lowering of the values in the Gros* and Kunkel tests, as well as of the serine/globulin ratio (especially in one dog), a reduction in the fibrinogen level, of the blood lipids, of total cholesterol, free and ester, of the ester to total (E/T) ratio, and of the sulfophosphovanillic (S.P.V.)† reaction. The animals had lost 2.6 Kg. and 1.3 Kg., respectively.

A biopsy performed at this time in one dog revealed that there were no gross lesions, but only modifications of the mitochondria.

The peanut meal content of the diet was then raised to 400 Gm. per day during the month of October, then to 500 Gm. during November, while the amount of bread in the regimen was reduced to 125 Gm. and then to 100 Gm.; that of meat was reduced to 100 Gm. and then eliminated during these two periods. In October, the ration thus comprised approximately 230 Gm. of protein and 170 Gm. of carbohydrate, and in November the respective amounts were 260 and 200 Gm.

Under the influence of this change in diet, the functional tests rapidly became much more abnormal. In addition, the residual serum nitrogen became significantly elevated, bilirubinemia was detectable in one of the dogs, and carbohydrate tolerance tests became obviously pathologic.

By the beginning of December, the two animals had lost 7.5 Kg. and 7.3 Kg., respectively. One died on December 4, 1950; the other was sacrificed on the following day.

The histologic examination of the liver of these two animals revealed a significant fatty degeneration, with marked hyperplasia of the reticulum (Figs. 1 and 2). The kidneys appeared to be quite normal in both dogs.

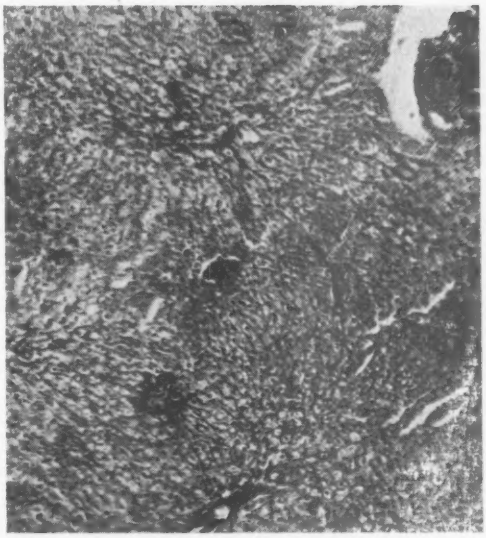

Fig. 1. Architectural destruction. Beginning periportal fibrosis (hematoxylin-eosin).

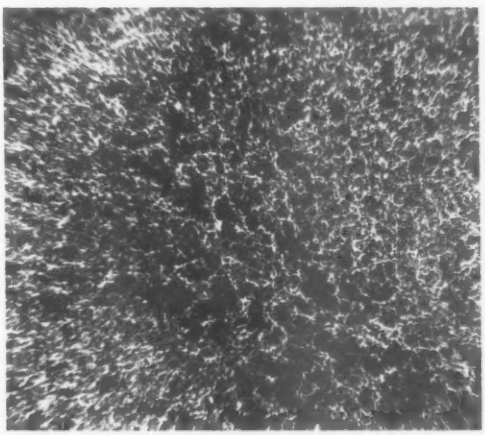

Fig. 2. Diffuse fatty infiltration (demonstrated with cerol B).

2. Dogs Fed on Soya Residue Meal

The experiments were conducted in a similar fashion. Two dogs (3 and 4) were placed from June 9 to September 29, 1950 on a regimen comprising 170 Gm. of protein per day and 185 Gm. of carbohydrate, furnished by

* Lipid function test carried out by colorimetric determination of unsaturated fatty acids.

† A quantitative Takata-Ara reaction using Hayem's solution as the sole reagent. The serum is considered to be abnormal when flocculation occurs with less than 1.5 cc. of the solution.[22]

250 Gm. of bread, 200 Gm. of lean meat, and 200 Gm. of soya meal. These foods were supplemented with vitamins and 5 Gm. of sodium chloride.

The functional tests in these two dogs revealed, in late September, a lowering of the values in the Gros and Kunkel tests, as well as of the serine/globulin ratio, a fall in fibrinogen, in blood lipids, in the S.P.V. reaction, in total cholesterol, free and ester, in the E/T ratio, and, finally, in cholinesterase.

A liver biopsy done in one of the two animals on September 29, 1950 showed only minor changes of the mitochondria.

In October the two dogs received 125 Gm. of bread, 100 Gm. of meat, and 400 Gm. of soya meal; then, from the beginning of November, 100 Gm. of bread and 500 Gm. of soya meal—i.e., approximately 220 Gm. of protein and 183 Gm. of carbohydrate in October, and, later, 270 Gm. of protein and 200 Gm. of carbohydrate.

The liver function tests showed various degrees of further impairment, as compared with the findings at the end of September. Then, on January 11, 1951, a liver biopsy was performed which, to our great surprise, revealed the existence of significant lesions of steatosis (Fig. 3).

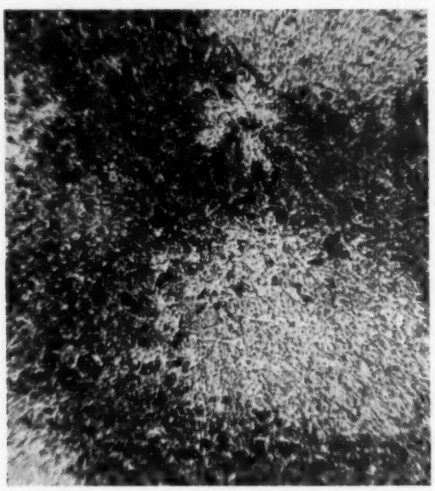

Fig. 3. Fatty infiltration having a stellate configuration (cerol B).

The dogs were kept on the same regimen as before.

In the following months, study of the functional tests showed no great change except with regard to the level of residual serum nitrogen, which rose significantly.

On April 12, 1951 a biopsy was performed on one of the animals (dog 3). Death occurred two days later. Examination of the liver revealed an accentuation of the process observed earlier, with evolution toward the appearance of an annular cirrhosis, with islets of compensatory hyperplasia with normal mitochondrial content (Fig. 4).

The other dog was left on the same regimen as before. He was not sacrificed until July; some of the biologic tests were improved (fibrinogen, lipidemia, S.P.V. reaction, cholinesterase); the others were unaltered. Examination of his liver revealed the existence of a periportal cirrhosis, but with signs of hepatic regeneration.

It is to be noted that in the two dogs fed on soya meal, as in the animals fed on peanut meal, the kidneys appeared macroscopically and microscopically normal.

3. Dogs Fed on Sunflower Seed Residue Meal

From June 9 to September 29, 1950, two dogs (5 and 6) received a diet composed of 250 Gm. of bread, 200 Gm. of lean meat, and 200 Gm. of sunflower seed meal, representing approximately 155 Gm. of protein and 185 Gm. of carbohydrate. These animals received supplementary vitamins and 5 Gm. of sodium chloride.

At the end of September, the study of the liver function tests revealed disturbances quite analogous to those which had been observed in the other dogs, but, taken as a whole, a little less pronounced.

A liver biopsy, performed by laparotomy in one dog (dog 5) on September 29, 1950, revealed only modifications of the mitochondria.

From the beginning of October, the two dogs received 125 Gm. of bread, 100 Gm. of meat, and 400 Gm. of sunflower seed meal. Then, beginning in November, they received

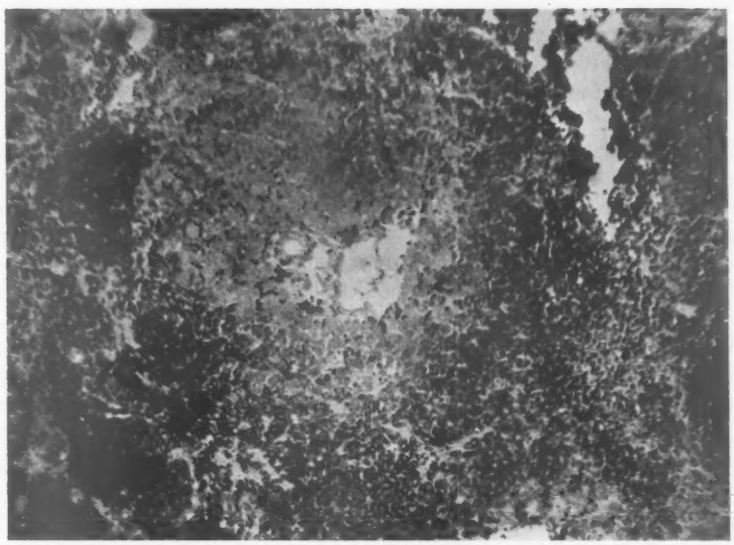

Fig. 4. In the islands of compensatory hyperplasia, the mitochondria are fairly normal in appearance; elsewhere they are nonexistent.

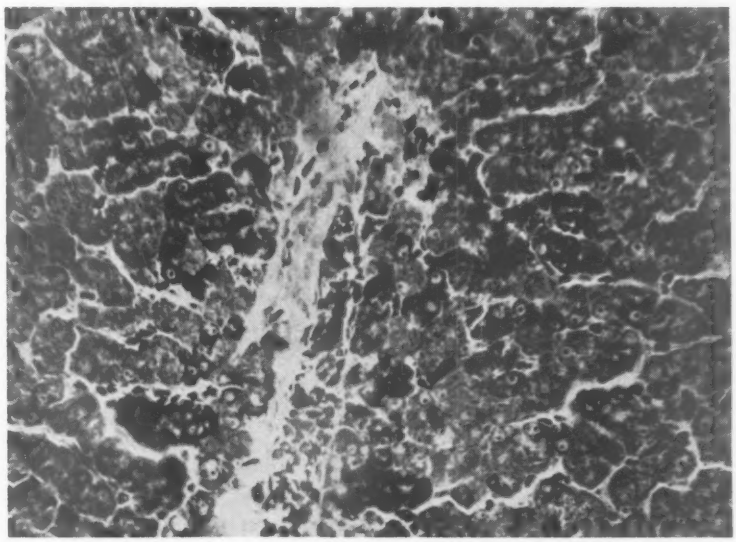

Fig. 5. Note the abundance of siderophilic cells.

100 Gm. of bread, and 500 Gm. of the meal or, respectively, 200 Gm. of protein and 500 Gm. of carbohydrate in October, and, subsequently, 245 Gm. of protein and 200 Gm. of carbohydrate.

The functional tests did not vary noticeably thereafter.

On January 11, a liver biopsy was done by laparotomy in one of the two animals (dog 6). This time it again revealed only mitochondrial modifications, notably a certain abundance of siderophilic cells (Fig. 5).

The experiment was continued under the same conditions. In the following months, the biologic tests remained as they had been previously. A biopsy was performed on April 18, 1951 in one of the two animals (dog 5). This led to death a few days later. The histologic examination enabled us to observe the beginning of periportal cirrhosis. In this animal the kidneys were macroscopically and microscopically normal.

The other dog was sacrificed on July 15, 1951. Examination of the liver revealed the same modifications of the mitochondria. The kidneys showed a rather marked sclerosis involving the peritubular tissue, Bowman's capsule, and the arterial vessels. It is very curious to note that in spite of these renal lesions, probably antecedent to the experiment, the animal tolerated a very high protein regimen without showing any hyperazotemia.

Discussion

Six dogs were maintained for three and a half months on a diet composed, in addition to vitamins and salt, of approximately 165 Gm. of protein and 185 Gm. of carbohydrate furnished by 250 Gm. of bread, 200 Gm. of lean horse meat, and 200 Gm. of peanut meal for two dogs (1 and 2), of soya meal for two others (3 and 4), and of sunflower seed meal for the last two dogs (5 and 6).

The study of liver function tests in all six animals revealed serum disturbances reflected particularly in the Gros and Kunkel tests, the serine/globulin ratio, the levels of fibrinogen, blood lipid, total cholesterol, free and ester, cholinesterase and S.P.V. reaction. Nevertheless, the liver biopsies revealed evidence only of modifications of the mitochondria, without any other lesion.

Later, the diet was modified. The meat was reduced, then eliminated; the daily bread ration was reduced to 100 Gm.; that of meal was raised to 400 Gm., then to 500 Gm. per day. Finally, the diet thus comprised 260 Gm. of protein to 200 Gm. of carbohydrate.

It should be noted that neither on this regimen nor the first did the animals take their entire ration regularly. But the proportions of these various constituents were those just specified.

Under the influence of the change in diet, great differences were observed in the animals. In dogs 1 and 2, fed on peanut meal, the liver function tests showed increasing and more widespread hepatic insufficiency. And, by the end of two months on the new diet, the livers of these two animals were the seat of extensive fatty degeneration with architectural destruction and hyperplasia of the reticulum.

The study of liver function in dogs 3 and 4, fed on soya meal, revealed a slower aggravation of the disturbances. A second biopsy, carried out at the end of three and a half months on the new regimen, nevertheless showed a marked steatosis involving the inner two-thirds of the lobules and forming an inextricable network. There was no cirrhosis.

Three months later, although the biologic tests showed no appreciable change, another biopsy carried out in one of the two dogs showed that the steatosis, now only slight, had given way to a true annular cirrhosis.

The other dog was sacrificed two months afterwards. Certain tests had improved; others were unaltered. Examination of the liver revealed the existence of a classical recent annular cirrhosis of the cellular type, with moderate hyperplasia of the reticulum and with mitochondrial signs of regeneration. In dogs 5 and 6, fed on sunflower seed meal, the biologic tests remained unaltered during the succeeding months. The liver biopsies done at the end of three months, and at six months and eight months after the change in regimen, showed only persistent modifications of the mitochondria, but no steatosis or sclerosis.

From these results there emerges, an important concept: one is struck by the lack of agreement between the exploratory liver function tests and the histologic lesions.

In the first part of these experiments the serum disturbances coincided with the modifications of the mitochondria in all three groups of animals. However, later on, if the serious and rapid hepatic degeneration in the dogs fed on peanut meal led to an accentuation of the signs of functional insufficiency, the much slower development of annular cirrhosis in the animals fed on soya meal did not produce serum disturbances much more accentuated than those which were observed in dogs fed on sunflower seed meal, and in whom the liver never showed anomalies other than those in its mitochondrial apparatus.

Furthermore, it is impossible to overemphasize the difference in the tolerance of the liver with respect to these meals, depending on whether they are derived from peanut, soya, or sunflower seed residue (all of which have practically the same protein content), and also, all else being equal, as to the proportions of carbohydrate and protein in the diet.

In the light of the recent findings on experimental dietary steatosis and cirrhosis, we wondered if the reasons for these differences in the toxicity of the three residues were not to be sought in their respective content of lipotropic substances.

Table I gives the amino acid composition of peanut, soya, and sunflower seed meal (after Jacquot and Merat[1]). As one can see, sunflower seed is much richer in methionine than soya, and this is richer than peanut. However, peanut meal contains 1 Gm. per cent of methionine, which represents, in the regimens we gave our dogs, a ration of 4 to 5 Gm. per day, more than is necessary in the daily diet of man.

TABLE I
Amino Acid Content of Soya, Peanut, and Sunflower Seed Residue Meals (Gm. per 100 Gm. of Meal)

Amino acids	Soya	Peanut	Sunflower
Arginine	7.1	9.9	8.2
Cystine	1.9	1.6	1.3
Histidine	2.3	2.1	1.7
Isoleucine	4.7	3	5.2
Leucine	6.6	7	6.2
Lysine	5.8	3	3.8
Methionine	2	1	3.4
Phenylalanine	5.7	5.4	5.4
Threonine	4	2.4	4
Tryptophane	1.2	1	1.3
Tyrosine	4.1	4.4	2.6
Valine	4.2	8	5.2

In addition, we put one dog (7) on a regimen comprising 100 Gm. of bread and 400 Gm. of peanut meal. The animal ate poorly, and we tried to improve his soup by making it with: 100 Gm. of bread, 100 Gm. of meat, and 250 Gm. of meal. Finally, however, we had to force-feed the dog by giving him each day a pap composed of 250 Gm. of peanut meal and 125 Gm. of sugar. Throughout the experiment the ration was supplemented with vitamins A, B, C, D, E, and K, with 1 Gm. of methionine, 2 Gm. of choline, and 0.50 Gm. of inositol per day. The animal died at the end of 40 days. The histological examination of the liver showed considerable disturbances. There were no renal lesions.

The reason for the much more rapid evolution of the histologic lesions in this animal than in our other peanut-fed dogs escapes us. The sensitivity of the liver to peanut proteins is, furthermore, variable from one dog to another.

Nevertheless, the lipotropic factors had no effect in modifying the degenerative process caused by this diet.

Inspection of the table showing the content of the various amino acids in peanut, soya, and sunflower seed meal does not seem to reveal differences such as would explain the mechanisms of the hepatotoxic action of these various meals.

Jacquot and the American authors, taking as the basis for estimation of the ideal nutritive value the composition of egg white, have calculated a deficit percentage of 76 for the peanut, 51 for soya, and 47 for sunflower seed. This is certainly the same order as that of the gravity of the experimental hepatitides we have observed. But between the quasi-innocuousness of sunflower seed and the serious toxicity for the liver of soya and peanut, there is a greater difference than is suggested by these figures.

Are there toxic substances in soya and peanuts? One of us, with Castagnou,[8] had already posed the question with regard to the peanut, from which Mooser,[13] in 1905, believed he had been able to isolate an alkaloid capable of causing paralysis and somnolence. But our investigations have not enabled us to confirm this work.

The residue meals were in all cases throughout our experiments incorporated in soups and cooked with these for 15 to 20 minutes at the most. One may wonder if heat does not modify the composition of these meals in different ways, according to whether they are derived from peanut, soya, or sunflower seed. The investigations of Mitchell, Burroughs and Beadles[14] have demonstrated that grilling peanut seeds at 200° does not modify the protein value of the residue. Osborne and Mendel,[15] and Jacquot, Matet, and Fridenson[2] have shown that *raw* soya is a very mediocre food and can produce various toxic effects, in particular goiters in the rat[16] or the chicken[17] and rapidly fatal hepatic lesions.[18] Once cooked, however, its biological value and its innocuousness are much greater. Finally, Jacquot, Matet, and Fridenson[2] have shown that sunflower seed does not lose its protein value after exposure to high temperatures during extraction of the oil.

The reason for the toxicity of the proteins of peanut and soya escapes us. However, on the practical level, their toxicity for the liver is now a well-established fact. It even enables us easily to achieve a pure, toxic, experimental hepatitis, without associated nephritis. It follows, then, that these meals should not be used in large amounts for the nutrition of man and animals. They are not tolerated except in small amounts and when accompanied by large quantities of carbohydrate. In the patient with liver disease, especially the cirrhotic, they certainly are not to be recommended. Even sunflower seed meal should not be used by these patients, except with caution.

Summary

In large amounts, peanut residue meal produces lesions of a rapid fatty degeneration of the liver; soya meal causes a similar process, although a slower one, which leads eventually to the development of a classic annular cirrhosis; sunflower seed meal leads only to modifications of the mitochondria. These three foods cause the appearance of serum disturbances, easily demonstrated by liver function tests.

The addition of lipotropic agents to peanut meal administered *ad libitum* does not decrease its toxicity.

Meals made from the oil-free residues of peanut, soya, and even sunflower seed are not to be recommended in the dietary of patients with liver disease.

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Resumen

Efecto de regímenes ricos en proteínas vegetales sobre el hígado de los perros

Ingerida en grandes cantidades, la harina hecha del resíduo de cacahuetes produce lesiones de rápida degeneración grasienta del hígado; la harina de soja causa un proceso similar, pero mucho más lento, que conduce, por último, al desarrollo de una cirrosis anular clásica; la harina de helianto sólo induce modificaciones de los mitocondria. Estos tres alimentos provocan la aparición de disturbios séricos fácilmente demostrables por las pruebas de función hepática.

La adición de substancias lipótropas a la harina de cacahuetes administrada *ad libitum* no disminuyó su toxicidad.

Las harinas hechas de los resíduos de cacahuetes, de soja, y aún de helianto no se recomiendan en la dietética de pacientes con afecciones hepáticas.

Editorial

Thoughts of the Season

Medical literature is a very impersonal means of communication. In our scientific objectivity we go out of our way to be not only first-person-plural but preferably inanimate. This is a distinct loss, for the warmth of the personal word captures the spirit as well as the sense of the message.

These reflections seem particularly apt now at the Holiday Season. Over the centuries, the fortnight ending with the start of the new year has been a period of reflection, appreciation, and resolution. Among other things, we suddenly communicate (by sending attractively decorated cards to people we may know only slightly), because we want all our friends and acquaintances to know that we are thinking of them—and that we are glad to have them in our ken.

It is in this spirit that we want to break the cool objectivity of medical publications and reach out to our readers and tell them how much we appreciate their interest in this JOURNAL. Through letters and personal conversations we know that many have a warm spot in their hearts for the *A. J. C. N.* We bask in that glow. And we of the editorial and publishing group want to take this means of speaking personally to each of our readers and sincerely wishing them a most happy Holiday, and a New Year of peace, pleasure, and plenty.

—S. O. W.

The Endocrine Glands and Nutrition

That ultimate in malnutrition—anorexia nervosa—so closely resembles hypopituitary "cachexia" (Simmonds' disease) that elaborate clinical and laboratory techniques are needed to distinguish them,[1] if, indeed, they are distinguishable. This nosological problem stems from the interrelationship between nutrition and the endocrine glands.

In an excellent review, Zubirán and Gómez-Mont[2] described their study of 529 adults suffering from chronic malnutrition in their hospital in Mexico City. Involution and atrophic changes in various endocrine glands were seen in the material obtained from 195 autopsies.

Malnutrition may be said to have a significant direct effect on the pituitary; and the resulting decrease in function leads to disturbances of other endocrine glands. The significant feature of this "malnutrition hypopituitarism" is that it is reversible by nutritional rehabilitation.[1,2] Thus, as a result of refeeding, a patient with "anorexia nervosa" gained 23 pounds. During this period there was a rise in radioiodine uptake, basal metabolic rate, serum cholesterol level, and in the excretion of 17-ketosteroids, corticoids, estrogens, and gonadotropins in the urine.

It is interesting that decreased gonadal function is usually the earliest endocrine manifestation of significant inanition. In fact, a large literature has grown up correlating amenorrhea and low urinary estrogen and gonadotropin excretion with malnutrition. The ovarian failure is believed to be secondary to hypopituitarism.

During nutritional recovery, on the other hand, estrogen excretion is usually increased. This is a transitory phenomenon, but sometimes may be of great magnitude. Significant increases in gonadotropin excretion were also observed during recovery,[2] and seemed to precede the hyperestrogenism. Because of the temporal relationship between these events and the re-establishment of ovarian function in women or the development of gynecomastia in men, it would seem that these changes are a phase in the rise of the pituitary-gonad axis to a higher level of activity.

Recovery by refeeding also helps to distinguish "functional" hypopituitarism, if you will, from "organic" hypopituitarism. Conversely, there is a notable lack of response to hormonal replacement therapy in malnutrition hypopituitarism. In fact, Perloff *et al.*[1] suggest that hormone therapy may be not only "of no specific value but may actually be contraindicated, as the decrease in endocrine activity appears to be an adaptive mechanism for the conservation of energy necessitated by the reduced caloric intake."

Still another illuminating aspect of this interrelationship is mentioned by Zubirán.[2] Care must be taken in evaluating the results of certain animal experiments, in which effects ascribed to endocrine manipulations may result from the accompanying nutritional disturbance, and, contrariwise, nutritional experimentation must consider secondary endocrinopathies.

—S. O. Waife, M.D.

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In Defense of Teleology

"It is evident that our whole unifying concept is based upon teleologic thought, that is, the principle of purposeful causality. It is difficult to understand why, among representatives of the exact sciences, and even among biologists and physicians, there is so much resistance to the use of teleologic arguments. Still we must admit that many of the most outstanding investigators of our time believe that one can—and indeed should—merely register scientific observations, refraining from all considerations of causality. I cannot follow such arguments. To my mind the sensation of causality is inherent in the structure of the human brain. Understanding itself is but the feeling of having securely attached a thing to our treasury of known facts, by solid bonds of obligatory sequences. . . .

"We sense a Creator, mainly because we and our surroundings strike us as being 'complex' and, during the short life-span of man, he sees no really complex structure being built up by chance, without the catalytic influence of a Maker. Why doubt, however, that in the span of ages, the organizing effect of a centralizing teleology could eventually build up awe-inspiring complexities, such as a planet, a tree or even ourselves? . . .

"Teleologic thought does not necessarily have to lean upon a purposeful Creator. . . . What we must clearly realize in biology is that teleologic analysis is applicable to any unit of creation, even after it is made.

"Science cannot and should not attempt to embrace the purpose of the original Creator, but it can and constantly must examine teleologic motives in the objects of creation, since only this can lead to understanding, as opposed to a mere accumulation of unintelligible facts."

—Hans Selye. *Texas Reports on Biology and Medicine* 12: 415, 419, 1954.

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The AMERICAN BOARD OF NUTRITION *announces the certification of* Dr. A. E. Schaefer *and* Dr. T. B. Van Itallie *as* Specialists in Human Nutrition. *The board will hold the next certifying examinations during April 1955, at locations convenient for candidates. Completed applications of persons who wish to be considered for certification should be in the office of the Secretary not later than February 1, 1955. Application forms may be obtained from the Secretary, Otto A. Bessey, Department of Biochemistry and Nutrition, The University of Texas School of Medicine, Galveston, Texas.*

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RICHARD W. VILTER, M.D., *Chairman*

The January-February issue of this JOURNAL (Vol. 3, No. 1) will present the full text of the papers read, together with the ensuing discussions, as a special SYMPOSIUM NUMBER.

Dietotherapy

DIET DURING PREGNANCY

By BERTHA S. BURKE, M.A.*

NUTRITION is generally recognized as an environmental factor which deserves consideration as an important part of prenatal care. The physiologic processes of the body are greatly altered during pregnancy and additional demands are imposed on the maternal organism. Digestion and absorption from the intestinal tract are often impaired in the early months of pregnancy and nutritional requirements are considerably elevated, especially in the later months of pregnancy. Pregnancy is a period of additional stress and for these reasons it is not strange that evidences of nutritional deficiencies are more likely to appear at this time. Thus it is obvious that a woman's nutritional status should be evaluated and dietary advice offered from as early in pregnancy as possible. Ideally, young women should be educated so that they understand the importance of entering pregnancy in good nutritional condition.

This article will discuss the nutritional requirements of the pregnant woman and how these may be met by diet. The nutritional allowances for pregnancy (last trimester) as recommended by the Food and Nutrition Board of the National Research Council are given in the following table:[1]

RECOMMENDED DAILY DIETARY ALLOWANCES

Nutritional essentials	Normal non-pregnant woman*	Pregnancy 3rd trimester
Calories†	2300	add 400
Protein (Gm.)	55	80
Calcium (Gm.)	0.8	1.5
Iron (mg.)	12	15
Vitamin A (I.U.)‡	5000	6000
Thiamine (mg.)	1.2	1.5
Riboflavin (mg.)	1.4	2.0
Niacin (mg.)	12	15
Ascorbic Acid (mg.)	70	100
Vitamin D (I.U.)		400

* These requirements are for a woman weighing 55 Kg. (121 lb.) and having a height of 157 cm. (62").

† Energy requirements vary with activity, size of person, etc.

‡ The requirement for vitamin A may be less if it is provided as vitamin A and may be more if it is taken chiefly in the form of carotene.

These allowances were designed to serve as guides and include a margin of safety over minimum requirements. They are based on the assumption that a woman enters pregnancy in excellent nutritional condition. When the diet has not been good previous to pregnancy, as is often the case, it should be improved to the recommended levels as soon as pregnancy is known. The recent revision of the Recommended Daily Dietary Allowances of the National Research Council states that these increased allowances are only for the third trimester of pregnancy. However, there is considerable basis for recommending the suggested increases for the latter half of pregnancy.

The diet needed during pregnancy is a more special one than is generally appreciated, because as pregnancy advances the requirements for protein, minerals, and vitamins are increased considerably more, percentage-wise, than is the caloric requirement (see table). For example, the caloric requirement increases only approximately 20 per cent, while the need for protein is increased approximately 45 per

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cent, for calcium 100 per cent, and the increased need for riboflavin closely parallels the protein increase. *It takes approximately 2000 calories of very carefully selected foods to meet the daily increased needs for nutrients other than calories.* This means that a woman's free choice of food is considerably narrowed during pregnancy, if the important structural and regulatory foods are to be eaten in optimum amounts daily. The nonpregnant woman can obtain her normal needs for these nutrients in about 1200 calories, to which must be added almost another 1000 calories in food to meet her daily energy requirement under normal conditions, i.e. if her weight is "desirable" for her and if her daily activity is considered to be "moderate."

Caloric requirements vary widely with activity and must be adjusted to individual needs. The pregnant woman should be expected to gain 20 to 25 pounds above a desirable weight for her height and build.[2] This implies that the underweight woman should gain more. The overweight woman's diet should be controlled carefully by restricting her calories only while her protein, mineral, and vitamin needs are fully provided.

Daily Diet During Pregnancy[3]

Here is a summary of the foods or their nutritional equivalents which should be taken daily during pregnancy:

Food Nucleus to Insure Optimum Nutrition During Pregnancy

Food	*Amount*	*Protein (Gm.)*
Milk, whole	4 glasses (8 oz.) (1 quart). (Patient should label own and see that entire quart is taken each day.)	32
Meat (lean), poultry, fish, liver is desirable at least once each week, cheese	2 servings/day, in all at least 4–5 oz. or equivalent in grams of protein	25–30
Egg	One	6
Fruit	At least 2 servings. Two servings of citrus fruit or equivalent should be eaten. (1 serving = 4 oz. orange juice, 1 med. orange, 8 oz. tomato juice, or ½ med. grapefruit.)	2
Potato	1 medium (150 Gm.)	3
Other vegetables cooked and/or raw	2 or more servings (1 serving = ½ cup). Dark green leafy or deep yellow vegetables often.	3
Bread and cereal	3 to 4 servings. (1 serving = 1 sl. bread or ½ cup cereal.) Whole grain or enriched.	6–8
Butter or fortified margarine	1 tablespoon	
Vitamin D	An amount to supply 400 I.U.	
		77–84

The above foods in the amounts suggested supply approximately 2000 calories and approximately 80 grams of protein. Additional food—either more of these foods or others of the patient's own choice—will be needed if she is underweight and may be necessary if she is of normal weight to furnish sufficient calories to produce the desired weight gain.

Meal Plan and Sample Menu

A meal plan and sample menu are given to illustrate how the necessary foods can be supplied in simple daily meals.

Meal Pattern	Sample Menu
Breakfast	
Fruit	Orange juice, 4 oz.
Cereal and/or bread and butter or fortified margarine	Oatmeal, ½ cup and/or toast, 1 slice and 1 tsp. butter
Egg	One
Milk	Milk, whole, 8 oz. (part on cereal)
Coffee or tea	Coffee
Luncheon	
Main dish (protein)	Sandwich of cold sliced meat (lean) and/or American Cheddar cheese
Bread and butter or fortified margarine	2 slices bread, 1 tsp. butter
Vegetables	Salad, tomato and lettuce
Milk	Milk, whole, 8 oz.
Fruit	Grapefruit, half

Dinner	
Meat (lean) or equivalent	Hamburg, lean, 4 oz.
Potato	Potato, 1 medium, baked
Other vegetables	Peas, 1/2 cup; carrots, 1/2 cup
Butter or fortified margarine	Butter, 1 tsp.
Milk	Milk, whole, 8 oz.
Fruit or simple dessert	Custard
Between Meals	
Milk	Milk, 8 oz. or the remainder of the quart if not taken with meals

Again, the woman of normal weight *may* and the woman who is underweight *will* need to eat more of these foods, as well as other foods of her own choosing, in order to gain to a desirable weight. For example, she may want both cereal and bread and perhaps bacon and jam at breakfast. At noontime she may want more than one sandwich or she may prefer to eat a dinner-type meal. She can have a higher caloric fruit or a dessert, such as custard or ice cream, at both luncheon and dinner. If her appetite is small, she may prefer to have four to six smaller meals in order for her to consume the necessary amount of food.

If weight gain is too rapid, the patient should be carefully instructed in the foods which she should not eat. She should be instructed to avoid foods rich in fats, sugars, and starches, such as gravies, bacon, mayonnaise, and other salad dressings, fat meats, doughnuts, potato chips, macaroni, spaghetti, rice, pies, pastries, cakes, rich puddings, ice cream, candy, all soft drinks, alcoholic beverages, popcorn, nuts, and the like.

In teaching our patients, we have found it important to explain why certain foods called the "essential foods" are necessary, and it is also equally necessary to explain any food restrictions. In this way we not only help the patient to understand the diet recommended for her but often list as well the foods she is to avoid.

Total Liquids

For the normal pregnant woman, fluid intake should be adequate, approximately two quarts of total liquid daily. This includes milk, fruit juices, tea, coffee, water, etc. Any change from this should be upon the advice of the physician caring for the patient.

Salt

Iodized salt should be recommended, especially in regions where goiter is endemic. Under normal conditions salt may be eaten in moderate amounts, but excessive use should be avoided. Common foods high in sodium content are bacon, ham, salt pork, salt fish, chipped beef, and other salty prepared meats, sauerkraut, dark rye bread, potato chips, pretzels, popcorn, pickles, olives, and the like. Certain vegetables, such as beets, celery, certain greens, as beet greens and dandelion greens, are high in sodium content; so also are canned vegetables. Most frozen vegetables have added salt.

Sodium bicarbonate ("Soda") should not be taken by the pregnant woman.

Further restriction should be upon the advice of the physician caring for the patient, and his instructions should be followed implicity. When weight gain is too rapid and/or when a patient shows symptoms of toxemia, and in certain other conditions, the physician may further restrict the sodium content of the diet. He may instruct the patient to use no added salt either at the table or in cooking, or he may wish the patient to have further instruction in regard to a low sodium diet.

General Considerations

In a practical and intelligent nutritional approach to the pregnant patient, much can be accomplished from a preventive standpoint if her physician at her first prenatal visit (which should be early in pregnancy) discusses with her: "What is a desirable nonpregnant weight for you?" Having established such a weight on the basis of build, he can then discuss what she should weigh at delivery. From this point on, the nutritional approach to the patient proceeds on the basis of a diet to provide the necessary amounts of protein, minerals, and vitamins to safeguard to the best of our present knowledge the health and course of pregnancy of the mother and the development and

health of the fetus. The physician, nurse, or nutritionist who is to handle her diet will have to spend sufficient time with the patient to motivate her to want to improve her food habits, when indicated, by explaining the possible benefits to both herself and her unborn child.

When a patient's protein needs are met by the essential foods already suggested or their equivalents in nutritional value, all other nutrients except ascorbic acid, vitamin A, and vitamin D will be provided in reasonably good amounts because of their natural association with protein in food. Protein is also one of the nutrients easy to check for clinical purposes, so that the amount usually consumed can be ascertained. When protein is deficient in the diet of the pregnant woman, her calcium and phosphorus, iron, riboflavin, and other B-vitamins will usually be deficient also. If her protein is not supplied by her daily food, she has no other possible way of obtaining it. She needs approximately 80 grams daily. Her increased requirement for protein has been shown repeatedly by the nitrogen balance studies of Hunscher and Macy[4] and others. These studies indicate that a woman normally stores 200 to 400 Gm. of nitrogen over and above that needed by the fetus and its adnexa. This storage of protein starts at about the eighth week of gestation and continues until close to term. It approximates 1250 to 2500 Gm. of protein, in addition to 850 to 900 Gm. which represent the total net requirement of the fetus. These figures represent an increase of 10 to 20 Gm. of protein over and above the normal nonpregnant woman's daily requirement. Our studies have shown that only 10 to 15 per cent of the women interviewed were taking the needed amount of protein; in fact, 15 to 20 per cent were taking less than 45 Gm. when first seen in the prenatal clinic.[5]

While the cause of toxemia of pregnancy is still a controversial subject, it is generally accepted that a well-balanced high protein diet acts as a preventive measure. The work of Hamlin[6] in Australia and our own work in the toxemia clinic of the Boston Lying-in Hospital (a preliminary report of this work has been published)[7] have demonstrated the preventive aspects of the nutritional control of toxemia. In both of these preventive programs, attention to the diet of the mother, together with attention to her weight gain, so that it was gradual throughout the course of pregnancy, were especially important.

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Nutritional Quotes

Definitions

"Diet means the food as taken regularly by an individual, and it is most desirable to place the emphasis on the diet of healthy persons as distinct from that prescribed for diseased persons. Nutrition is the sum of the processes concerned in the growth, maintenance and repair of the living body as a whole or of its constituent parts. Thus diet and nutrition are entirely different and the terms should not be confused."
—H. R. Sullivan and N. E. Goldsworthy. *The Medical Journal of Australia* 41 (4): 136, 1954.

Outlook and Intake

"If we regard the individual's relationship to food as an example of his relationship to the environment, we find an interesting correlation. Those who are energetic and deal with the environment directly have the same type of relationship to food; they attack it, they devour it, and they enjoy so doing. They have many contacts with the environment: they are socially active, express aggression directly through complaint or argument; they implement their capacity for activity in current interests and plans for the future. Those who have a lowered food intake tend to shrink from direct contact with the environment; they are lonely, withdrawn, rather depressed people. Their anger and dissatisfactions are not expressed in direct fashion, but obliquely."
—Elias Savitsky, M.D.: Psychological Factors in Nutrition of the Aged, in *Social Casework*, December 1953.

Sweets to the Sweet

"Sugar has a well-known 'sweet' taste, an expression often used to define a degree of pleasantness in food. The acceptability of sugar has been shown to be related to the level of blood sugar. Human subjects with a normal blood sugar level rejected a 30% solution of sucrose as 'sickeningly' sweet, but it became, instead, quite acceptable as a 'long drink.' . . . Thus, there was established a direct relationship between the acceptability of a 30% sucrose solution and the physiological state of human subjects, specifically, in this case, the blood sugar level. In other words, a state of stress (namely, a low blood sugar) rendered the sugar solution acceptable, whereas in the same individuals not under this specific stress the same sugar solution was unacceptable."
—Samuel Lepkovsky. *Advances in Food Research, Vol. IV*, Academic Press Inc., New York, 1953, p. 124.

Food and Teeth

"Mellanby's (1934) experimental evidence clearly indicates that nutritional conditions are possible which will interfere with the formation of normal teeth. However, there is no unanimity about the direct association between imperfect structure and the occurrence of caries. Indeed, there is evidence that imperfectly formed teeth may remain relatively free from caries, just as teeth of apparently good structure may decay rapidly. The answer to this paradox appears to lie in the nature of the oral environment to which the two types of teeth are subjected after eruption. Thus it has been observed that a nutritionally deficient diet is compatible with a high resistance to dental caries. . . . In short, whilst nutrition can be related to structure, it is not necessarily related to freedom from or susceptibility to caries."
—H. R. Sullivan and N. E. Goldsworthy. *The Medical Journal of Australia* 41 (4): 137, 1954.

No Food Is "Natural" Food

"The time, if ever, when all our foods will consist of purified nutrients seems distant indeed; but we shall probably continue, nevertheless, to supplement our food with pure nutrients in ever-increasing amounts. The source of the bulk of our food still consists of living tissues—or derivatives of living tissues—of plants, animals, or micro-organisms, all of which are basically similar in chemical composition, since they all contain essential nutrients such as minerals, vitamins, fatty acids, and amino acids. It should be realized, however, that these living tissues were not meant to be food for animals. For example, the wheat grain was meant to produce more wheat—not to be made into a loaf of bread; and fish were meant to produce more fish—not to be put into a can or frying pan, for eating."
—Samuel Lepkovsky. *Advances in Food Research, Vol. IV*, Academic Press Inc., New York, 1953, p. 106.

The Still Puzzling Role of Vitamins

"In each case in which a definite function can be assigned to a particular vitamin it has been found to serve as an important part of one or more coenzymes. Yet, although it is known, for example, that thiamine, as thiamine pyrophosphate, is necessary for the metabolism of pyruvic acid and it is clear that a deficiency of thiamine results in some interference in the metabolism of this three-carbon intermediate, it cannot be stated just how this metabolic lesion leads to the signs and symptoms of vitamin deficiency."
—C. A. Villee. *New England Journal of Medicine*, 251: 21, 1954.

Reviews of Recent Books

Protein Metabolism by R. B. Fisher, Methuen & Co., Ltd., London, 1954, pp. 198, $2.50.

This little book of 192 small pages is a good concise summary of protein metabolism with emphasis on amino acids. Rather than cover the entire field, the author has limited his discussion to a few pertinent subjects. The chapter on the use of isotopes in the study of protein metabolism presupposes some familiarity with the subject matter, but presents a dynamic picture of the "metabolic pool." Endocrine interactions are briefly described. There is an excellent chapter on the nutritive value of proteins which leans heavily on the 1946 review article by R. J. Block and H. H. Mitchell.

Perhaps the best feature of the book is the emphasis on what is known as distinct from what is believed or interpreted. The author rightly reminds us also of our tendency to suppose that the latest is the best, which "tends to induce some disproportion in the thinking of both writer and reader." This approach is unusual and welcome.

Each chapter has a brief "conclusion" at the end which recapitulates the points made earlier. There is an index and a number of clear figures are included.

Although the title may suggest a complete treatise on the subject and therefore may be misleading, the book does achieve its aim of presenting a new viewpoint on certain facets in this wide field. S.O.W.

Food Selection and Preparation (fourth edition) by Marion Deyoe Sweetman and Ingeborg MacKellar, John Wiley & Sons, Inc., New York, 1954, pp. 645, 47 illustrations, 65 tables, $6.50.

The subject of food from the store to the plate is covered in four sections. Section I includes a presentation of the basic standards for the appraisal of foods: nutritive quality, digestibility, sanitary quality, palatability, and economy. The techniques of food preparation and preservation are covered in two chapters of Section II, followed by a discussion in Section III of the structure of food materials. The seven chapters of Section IV are devoted to the selection and preparation of foods: fruits and vegetables; milk and its products; eggs; meat and allied foods; fats and oils; sugars and food mixtures high in sugar; grains and their products.

Diagrams, charts, and photomicrographs showing the effects of various procedures in food preparation effectively clarify and extend the information given in the text. The sixty-four tables throughout the text are worthy of careful study. They contain a wealth of information concerned with the nutritional contributions of foods, data on per capita consumption, time-temperature charts in food preparation, the effects of various methods of processing on nutritional quality and palatability, and many others. An additional table in the Appendix gives the nutritive values of household quantities of foods.

This reviewer considers the text especially noteworthy for the emphasis and motivation which is provided throughout for the preservation of the nutritive qualities of foods, as well as the maintenance or enhancement of the wholesomeness and palatability of foods.

This text can be highly recommended for use in food preparation courses in colleges of Home Economics. An elementary knowledge of organic chemistry is essential for the more technical aspects of the discussion, but selected portions may be used satisfactorily in first courses of foods by students who have had no chemistry. The book will prove to be a most useful reference for the dietitian and home economist. C.H.R.

Experimental Diabetes and Its Relation to the Clinical Disease. A Symposium Organized by The Council for International Organizations of Medical Sciences, edited by J. F. Delafresnaye, Charles C Thomas, Springfield, 1954, pp. 337, $5.50.

Many of the world's leaders in metabolism and diabetes participated in a symposium organized on the occasion of the first congress of the International Diabetes Federation at Leiden, July 1952. The presentations and the following discussions are recorded in this interesting book. The authors include such authorities as Best, de Duve, Lazarow, Conn, Long, Cori, Lukens, Hagedorn, Hoet, and Young, among others.

Chapters are devoted to glucagon, alloxan diabetes, adrenal steroids, growth hormone, pregnancy, and heredity. All are thoughtful essays covering the latest information on a current problem. The recorded discussions are particularly stimulating. As R. D. Lawrence says, "the twin sisters clinical observation and laboratory experiment walk very closely hand in hand in diabetes." The "diabetologist," the "metabolist," and the internist will be profitably rewarded by this volume. S.O.W.

Symposium on Problems of Gerontology. Proceedings of a Symposium held under the auspices of The Johns Hopkins University, School of Hygiene and Public Health and The National Vitamin Foundation, Inc., New York, March 2, 1954. By F. H. Bethel, B. F. Chow, C. S. Davidson, H. J. Deuel, Jr., D. J. Ingle, J. E. Kirk, A. I. Lansing, C. N. H. Long, H. A. Rafsky, and N. W. Shock. The National Vitamin Foundation, Inc., New York, pp. 141, paper, $2.50.

There is much highly nutritious intellectual meat in this collection of ten papers relating to the metabolic aspects of aging by active research investigators. As is inevitable, there is fragmentation of data into highly specialized areas, and the omission of a summary of the data and concepts presented is unfortunate. One may fail to see the forest by concentrating on individual trees.

Shock reports anent his studies on Vitamin A absorption in relation to age, age changes in glucose tolerance, in renal function and metabolism. Lansing discusses certain mechanisms of aging with rotifers, particularly with reference to maternal age and growth characteristics. Deuel presents very interesting data concerning sex differentials in fat metabolism. Davidson points out the role of endocrine control in protein metabolism in relation to the endocrine alterations which occur in senescence. Chow presents certain data relating to the utilization of Vitamin B_{12} with advancing age. Kirk reports upon blood and urine vitamin levels in various groups of people and discusses the pathogenesis of low values. Bethel presents his ideas anent hemopoietic factors with reference to aging, and Long considers the role of the adrenal cortical steroids in affecting metabolic activity. This is further elaborated by Ingle in a discussion of endocrine stress and the adaptation syndrome. Rafsky closes the discussion with a consideration of some of the special nutritional problems of the aged as observed and studied in a Home for the Aged.

This symposium is worthy of careful study by all those interested in clinical nutrition and geriatric medicine.

E. J. Stieglitz

Books received for review by the *American Journal of Clinical Nutrition* are acknowledged in this column. As far as practicable, those of special interest are selected, as space permits, for a more extensive review.

Vitamins in Nutrition and Health by Audrey Z. Baker, Staples Press, Inc., New York, 1954, pp. 147, $2.50.

Nieren-Clearance-Untersuchungen im Kindesalter by F. K. Friederiszick, S. Karger, Basel, 1954, pp. 112, Sw. fr. 14.55.

Clinical Approach to Jaundice by Leon Schiff, Charles C Thomas, Springfield, 1954, pp. 113, $3.75.

Roberts' Nutrition Work with Children by Ethel Austin Martin, Univ. of Chicago Press, 1954, pp. 527, $7.50.

Abstracts of Current Literature

THIAMINE METABOLISM

The metabolism of thiamine involves the conversion of this vitamin to a phosphorylated form, cocarboxylase, within the tissues. The phosphate groups present in the co-enzyme are derived from adenosine triphosphate (ATP). The possibility that vitamin D accelerates the conversion of thiamine into the physiologically active form, cocarboxylase, has been suggested. Furthermore, there is a possibility that an imbalance of members of the B-complex may disturb this conversion of thiamine.

On the Synthesis of Cocarboxylase in the Blood; Its Activation by Vitamin D. C.-E. Raiha and O.-A. Forsander. *Gaz. méd. France* 60: 57, 1953.

The mechanism by which thiamine is synthesized to cocarboxylase is not yet clearly understood; nor has the enzyme (transphosphatase) which catalyzes this process been isolated in its pure form. It has, however, been ascertained that the intestinal mucosa, liver, kidneys, brain, and blood cells contain large amounts of transphosphatase.

With pig's blood, active production of cocarboxylase from thiamine occurs *in vitro*, and it is this phenomenon which was studied in the experiments reported here. The quantity of cocarboxylase produced was calculated from the amount of CO_2 liberated in 30 minutes from pyruvic acid—which is decomposed by cocarboxylase.

Five ml. of pig's blood was incubated at 37° with 50 mg. thiamine, while simultaneous control experiments were run (a) without added thiamine; (b) with added thiamine and adenosine triphosphate (ATP). After 30 minutes, the cocarboxylase content of all the samples was measured. With the addition of thiamine, there was a 277 per cent increase of cocarboxylase over that in the control without thiamine, while a 300 per cent increase occurred in the sample to which both thiamine and ATP were added. Obviously then, the addition of ATP does not influence the process of phosphorylation to any great extent. When pig's blood is incubated with different quantities of thiamine, the quantity of cocarboxylase produced over a 120-minute period is directly proportional to the amount of thiamine introduced—but only up to a certain point. Beyond this, either the ATP reserve of the blood cells is depleted, or else the reactivity of the catalyzing enzyme is exhausted.

Although rather slow in the conditions of these experiments, the speed of cocarboxylase synthesis can be influenced by certain specific substances: testosterone retards it in the live mouse; several sympathomimetic amino acids slow it *in vitro;* and, according to Raiha, elevation of blood cocarboxylase occurs in subjects simultaneously injected with thiamine and vitamin D. The latter substance was tested in another experiment in which pig's blood containing thiamine with and without phosphorylated vitamin D was incubated at 37° for 120 minutes. In the

sample containing thiamine only, the cocarboxylase increased an average of 197 per cent; in the specimen containing vitamin D as well as thiamine, the cocarboxylase increased 239 per cent. There was, however, considerable variation in the results of the several experiments in this series.

The authors conclude that phosphorylated vitamin D accelerates the transformation of thiamine into the physiologically active form, cocarboxylase, and that this property should be borne in mind in cases of severe thiamine deficiency, particularly if a concomitant deficiency of vitamin D is suspected. It is suggested that further observations should verify whether the observed acceleration increases with age, and whether it occurs with substances other than thiamine.—C.-J. Howell

Comparative Action of Thiamine and Cocarboxylase in Beriberi Complicated by Vitamin Imbalances. M. L. Orabona. *Intern. Ztschr. f. Vitaminforsch.* 25: 170, 1954.

It has been suggested that imbalances among the B-complex vitamins may be due to competition for phosphoric acid or to disturbances of the normal processes of phosphorylation. In this connection, the author felt it would be of interest to see whether pigeons with beriberi complicated by vitamin imbalance would respond differently to cocarboxylase (phosphorylated thiamine) than to thiamine.

Thirty-eight pigeons were placed on a thiamine-free diet; 14 were given 10 mg./day of folic acid; 15 received 15 mg./day of niacin; and 9 controls received no other treatment.

Of the controls, with simple avitaminosis, all but 2 recovered on thiamine administration (these 2 died too soon after the injection to have been affected by it). Of the pigeons in which imbalance was induced by excessive folic acid, all those receiving thiamine died within 24 hours, while all those treated with cocarboxylase recovered; 4 were completely cured and one remained paretic.

Similar results were obtained in pigeons in imbalance through an excess of niacin: all but one receiving thiamine died, and the surviving bird remained paretic despite protracted thiamine therapy. Of the birds which received cocarboxylase, all but one (which died before the treatment could become effective) survived, 5 recovering completely on a single dose of 25 mg.

The data show clearly that while thiamine is ineffective in pigeons with beriberi and vitamin imbalance, cocarboxylase reverses the pathologic picture, even to the point of complete cure. Hence, the vitamin can acquire, in its phosphorylated form, a therapeutic power not possessed by the nonphosphorylated form. This observation seems to support the hypothesis of the importance of the processes of phosphorylation in the pathogenesis of vitamin imbalances. (An interesting analogy is the inability of folic acid to prevent the toxic effects of its antagonist, aminopterin, while folinic acid is able to reverse them—suggesting that the latter, and not folic acid, is the biologically active form.) It therefore seems likely enough that the phase inhibited by vitamin imbalance is actually that of phosphorylation.—C.-J. Howell

Reduced blood levels of cocarboxylase are described in patients suffering from neurocirculatory asthenia. This is of interest in view of the variations in lactic acidemia in this condition described by Paul White and co-workers several years ago.

The Cocarboxylase Content of Blood in Normal Subjects and in Various Diseases, Especially Neurocirculatory Asthenia. T. J. Vartio. *Scandinav. J. Clin. & Lab. Invest.* 5, Supplement 10, 1953.

Vitamin B_1 is catalytically active in the form of thiamine pyrophosphate or cocarboxylase. Vartio, at the University of Helsinki, carried out a careful study on the cocarboxylase content of the blood in 57 normal subjects and 440 patients suffering from various diseases. The normal values, by the method used, ranged between 11 and 21 μg./100 ml. with a mean of 14.9 $\pm$ 0.4 μg./100 ml. The cocarboxylase level did not depend upon age or sex. Variations during the day were very slight, and very little fluctuation was noted in any one subject. However, when the cocarboxylase level was studied in the course of a year, considerable variation was revealed.

In a wide group of cases, the cocarboxylase blood level was within the normal range. Among the diseases studied were diabetes, acute rheumatic fever, rheumatoid arthritis, peptic ulcer, colitis, carcinoma, asthma, tuberculosis, hepatitis, etc. The values were most clearly low in the patients suffering from neurocirculatory asthenia. The mean value of the group was 12 $\pm$ 0.4 μg. These figures are statistically significant compared to the mean normal value. In a group of obese patients, the mean was 17.2; for patients who were obese and hypertensive, 16.2; and when hypertension and diabetes were present in association with obesity, the value was 17.8 μg. These values are statistically higher than normal.

The cocarboxylase content of the blood in patients with leukemia was elevated, evidently due to the elevated leukocyte level.

When patients with neurocirculatory asthenia were given thiamine injections, no curative effects were noticed in the subjective symptoms in spite of an elevation in the blood cocarboxylase level. In as much as Kerppola, from the same University, in 1951 noted an increase in the alkaline phosphatase of the blood in patients with neurocirculatory asthenia, it may be possible "that in these patients alkaline phosphatase enhances the dephosphorylation of the cocarboxylase of the blood cells more than in normal cases."—S. O. Waife

Among the recognized actions of thiamine is the oxidative decarboxylation of pyruvate and alpha-ketoglutarate. The influence of thiamine deficiency upon the metabolism of these substances and of the sparing effect of fat upon thiamine deficiency is the subject of the following paper.

Pyruvate and α-Ketoglutarate Metabolism in Thiamine Deficiency. R. C. Wright and E. M. Scott. *J. Biol. Chem.* 206: 725, 1954.

Experiments are presented which compare the effects of thiamine deficiency on α-ketoglutarate oxidation and on pyruvate oxidation. The evidence presented supports the view that fat in the diet alleviates the symptoms of thiamine deficiency by allowing a more nearly normal metabolism, since the oxidation of fat unlike that of carbohydrate bypasses the oxidation of pyruvate. Using liver, kidney, heart, and brain homogenates of normal and thiamine-deficient rats, it was confirmed that the oxidation of pyruvate is depressed in thiamine deficiency and that this oxidation could be stimulated by the addition of thiamine pyrophosphate (cocarboxylase). In the same tissues, oxidation of α-ketoglutarate was not greatly lowered and no specific stimulation by addition of thiamine pyrophosphate could be demonstrated. This is interpreted as evidence that thiamine pyrophosphate is not a co-enzyme of α-ketoglutarate oxidation.—M. K. Horwitt

Several metabolic antagonists exist for thiamine which may have different modes of action as competitive inhibitors of the vitamin.

Studies on Thiamine Analogues. III. Effects on Enzyme Systems. S. Eich and L. R. Cerecedo. *J. Biol. Chem.* 207: 295, 1954.

Pyrithiamine, oxythiamine, and neopyrithiamine have been shown to be competitive inhibitors of thiamine when administered to animals. This report discusses the results of procedures designed to clarify the mode of action of these analogues of thiamine.

The decarboxylation of pyruvate and the formation of acetylmethylcarbinol by wheat germ carboxylase are inhibited by oxythiamine diphosphate. This inhibition is largely dependent upon the order of addition of the inhibitor and thiamine diphosphate to the enzyme. There is a lack of inhibition of the system by oxythiamine diphosphate when the analogue is introduced to the system after cocarboxylase, thus indicating a strong attachment of co-enzyme to apoenzyme. Three possible courses of action were considered as possibilities: (1) the inhibitor may block the synthesis of thiamine diphosphate from thiamine; (2) the inhibitor may itself be phosphorylated, and the resulting compound could in turn compete with thiamine diphosphate for the apoenzyme; and (3) the inhibitor may in some manner cause the displacement of thiamine from the tissue of the organism.

Oxythiamine and neopyrithiamine have no effect upon pyruvate decarboxylation. Acetylcarbinol formation is not influenced by the addition of oxythiamine. Neopyrithiamine, but not oxythiamine, is a very potent inhibitor of rat liver thiamine phosphorylase. In this case, order of addition of substrate and inhibitor is immaterial.—M. K. Horwitt

Other studies have discussed the metabolism of thiamine in relation to muscle and nerve tissue, urinary excretion, and adrenal hypertrophy.

Thiamine in Regeneration and Degeneration. H. Bowoden. *Ztschr. f. Vitamin-Hormon- u. Fermentforsch.* 6: 6, 1954.

The thiamine content of the muscle (guinea pig) decreases after sectioning of nerves or tendons. If muscle fibers are cut, the decrease is negligible and limited to the first two days. Regeneration of the sciatic nerve is accompanied by an increase of the thiamine content in the intact portion, appearing in the first four weeks only; this increase is more marked in the central part than in the portion nearest the point of section. In the tadpole (rana agilis), regeneration of the tail stump is associated with an increase of the thiamine content, occurring after 14 days. The regenerative process in nerves and muscles seems thus to involve an increase of thiamine in the tissues where the regeneration originates.—C.-J. Howell

Influence of Sodium Salicylate on the Urinary Elimination of Thiamine. M. Ramunni. *Acta vitaminol.* 8: 164, 1954.

Because of the similarity of the chemical structure of para-amino-salicylic acid (PAS) and that of sodium salicylate, and because the former has been shown to produce a marked and rapid decrease in the urinary elimination of thiamine, the effects of sodium salicylate on thiamine excretion were investigated in normal subjects and in patients. Since the results were negative, it is likely that the action of PAS in this connection is due to its possession of an amino group lacking in sodium salicylate.—C.-J. Howell

Correlation Between Blood Pyruvate, Tissue Thiamine, and Adrenal Hypertrophy in Thiamine Deficiency in the Rat. G. Rindi, G. Ferrari, and V. Perri. *Acta vitaminol.* 25: 210, 1954.

Recent studies have demonstrated the importance of tissue vitamin levels in determining the appearance and type of alterations occurring after various periods of vitamin deficiency. In thiamine deficiency, metabolic and functional changes occur only when the vitamin reserve is decreased below a certain

critical level; hence the interest of attempts to correlate tissue vitamin levels with metabolic alterations. The most striking metabolic change in thiamine deficiency is the increase of pyruvate in blood and tissues, and the authors sought specific correlations between increased blood pyruvate and decreased tissue thiamine in brain, muscle, and liver. They also investigated the degree of adrenal hypertrophy and variations in body weight.

The experiments were carried out on albino rats. After various periods of avitaminosis, the rats were decapitated and the pyruvate content of the blood determined by a modification of the Lu method. From a study of the tissues at various stages of thiamine deficiency, various facts emerged. The brain, in contradistinction to the other tissues, maintained its thiamine content almost constant during the first five days of deficiency. Muscle thiamine reached the minimal level before any of the other tissues (15th day) and remained at this level thereafter, whereas the thiamine content of brain and liver tissues continued to decline till the end of the experiment. The blood pyruvate level remained practically constant up till the 18th day of avitaminosis, after which it rose significantly till the end of the experimental period. Pyruvate accumulation is not, therefore, one of the earlier signs of thiamine deficiency; it occurs only when tissue thiamine levels are decidedly low. The increase in blood pyruvate showed a closer statistical correlation with the degree of adrenal hypertrophy than with the decrease of thiamine in the organs. It would seem that the accumulation of blood pyruvate results from heightened adrenocortical function (stress), which, as Skelton has suggested, is an accompaniment of thiamine deficiency. Body weight increased up to the 18th day, even though the tissue thiamine content was decreasing steadily and markedly, suggesting the presence of an ample initial reserve of the vitamin.—C.-J. Howell

PYRIDOXINE

Pyridoxine, in the form of pyridoxal phosphate, has been shown to serve as a co-enzyme for the decarboxylation and transamination reactions involving certain amino acids. Pyridoxine deficiency has been described in human subjects following the feeding of the metabolic antagonist to vitamin B_6, desoxypyridoxine, and during the feeding of pyridoxine-deficient diets to infants (see P. György: Vitamin B_6 in Human Nutrition, editorial, in J. Clin. Nutrition *2: 44, 1954). It has also been suggested, as early as 1934, that vitamin B_6 was required for the utilization of essential fatty acids. Recent studies have shown that rats receiving a pyridoxine-deficient diet grow at a reduced rate, the deficient animals being unable to develop deposits of body fat.*

Studies on Vitamin B_6. V. Chronological Sequence of Biochemical Defects in the Vitamin B_6-Deprived Rat. J. R. Beaton, J. L. Beare, G. H. Beaton, E. F. Caldwell, G. Ozawa, and E. W. McHenry. *J. Biol. Chem.* 207: 385, 1954.

Although a difference in body weight was apparent between deficient and control rats as early as the fourth day, the deprived animals did not reach a growth plateau until after four weeks of vitamin B_6 restriction. Since the deprived and pair-fed control animals consumed the same quantity of food and since absorption of protein, fat, and carbohydrate has been found to be normal in vitamin B_6-deficient rats, it would appear that those animals not provided with the vitamin were unable to utilize food materials with sufficient efficiency to meet energy requirements and to provide a surplus for anabolic purposes. Differences in carcass total crude fatty acids and tissue total vitamin B_6 levels were evident within one week of deprivation. Significant alterations in nitrogen metabolism were not evident until at least four weeks, when body weight, carcass total food fatty acids and tissue total vitamin B_6 values had attained constant levels. The results of this study indicate that disturbances in nitrogen metabolism in vitamin B_6 deficiency may be secondary to a primary effect on energy production which deprives the animal of surplus food for storage as fat. No alteration in the basal metabolic rate of vitamin B_6-deficient rats has been observed.—M. K. Horwitt

However, the following paper would indicate that vitamin B_6-deficient rats are able to form lipids from glucose at a normal rate and to conserve fatty acids.

Some Effects of Vitamin B_6 Deficiency on Fat Metabolism in Rats. H. S. R. Desikachar and E. W. McHenry. *Biochem. J.* 56: 544, 1954.

It has been shown that on a fat-free diet and pyridoxine supplementation, rats have a higher content of body fat than deficient animals. When fat was included in the diet, results have been conflicting. This paper discusses the role of pyridoxine in the metabolism of fat in the rat.

Using isocaloric feeding of two fat-free basal diets, one high in casein and the other in sucrose, it was shown that the total amount of fat in the livers of rats fed the casein diet was greater than in the livers of rats maintained on the sucrose diet, but deprivation of pyridoxine had no observable effect upon liver fat and in no case was there sufficient fat to warrant designation of a liver as fatty. A supply of linoleic acid did not apparently alter the quantity or quality of liver lipids.

All rats fed the casein diet had less carcass fat than did rats on the sucrose diet and this may have been due to a difference in food consumption. With both diets, lack of pyridoxine in the diet caused a decrease in the percentage of total fat in the carcass, an effect which was partially prevented by a supply

of linoleic acid. The proportion of phospholipids and the iodine value of total lipids were greater in deprived than in control animals. The data suggest that vitamin B_6-deficient rats conserve phospholipids and unsaturated fatty acids. Data on the incorporation of C^{14} (from glucose) suggest that synthesis of carcass lipids proceeded equally well in both control and deficient rats.—M. K. HORWITT

Pyridoxine deficiency has been shown to be associated with disturbances in tryptophane metabolism, resulting in an increased excretion of xanthurenic acid. Experimental evidence suggests that pyridoxal phosphate is the co-enzyme for kynureninase. The interrelations between certain hormonal deficiencies and tryptophane metabolism, as related to pyridoxine, are discussed in the following paper.

Experimental Observations on the Relationship Between Tryptophane, Pyridoxine, and Endocrine Glands. F. M. Chiancone, E. Ginouilhac, L. Mainardi, and L. T. Tenconi. *Acta vitaminol.* 7: 12, 1953.

Since pyridoxine deficiency is accompanied by a serious disturbance of tryptophane metabolism and since pyridoxine and endocrine function are interrelated, the possibility that tryptophane, too, may play a role in endocrine function deserves attention.

To explore this possibility, the authors gave a single oral dose of tryptophane (500 mg./Kg.) to hypophysectomized, adrenalectomized, or ovariectomized rats. Twenty-four hours later, the urines were analyzed (by paper chromatography) for the various metabolites of tryptophane. Parallel observations were made on non- or sham-operated rats and on intact and operated rats deficient in pyridoxine.

Removal of any of the three glands was found to result in reduction of the nonoxidized metabolites derived from kynurenine (anthranilic and kynurenic acids) and formation of 3-oxyanthranilic acid. Xanthurenic acid excretion *increased* after ovariectomy or hypophysectomy, *decreased* after adrenalectomy.

In pyridoxine-deficient rats to which the vitamin was subsequently administered, chromatography after tryptophane administration gave a normal picture except for the continued presence of 3-oxyanthranilic acid and a weaker response for kynurenic acid. Pyridoxine administration also caused oxykynurenic → xanthurenic acid metabolism to return to normal in rats not deficient in pyridoxine but which had shown variations in xanthurenic excretion as a consequence of hypophysectomy or adrenalectomy.—C.-J. HOWELL

Both pyridoxine deficiency and inanition in animals resulted in a significant fall in the circulating eosinophils.

Blood Eosinophil Levels in the Young and Adult Pyridoxine-Deficient Rat. L. C. Butler and A. F. Morgan. *Proc. Soc. Exper. & Med.* 85: 139, 1954.

Inanition and pyridoxine deficiency were evaluated in terms of effect upon the level of circulating eosinophils. Both pyridoxine-deficient and starved rats showed a significant fall in eosinophils as compared to the normally fed animals. It was concluded, therefore, that inanition is the common denominator in both groups.—L. W. KINSELL

In infants, pyridoxine deficiency has been found to result in convulsions which have been controlled by the administration of this vitamin in doses varying from 2 to 6 mg. Other nervous system changes have been ascribed to vitamin B_6 deficiency, in the form of neuritis occurring after the administration of isoniazid.

Pyridoxine Dependency: Report of a Case of Intractable Convulsions in an Infant Controlled by Pyridoxine. A. D. Hunt, Jr., J. Stokes, Jr., W. W. McCrory, and H. H. Stroud. *Pediatrics* 13: 140, 1954.

This is a very interesting and perhaps significant report of a case of recurring convulsions starting on the third day of life in an infant born of a mother with hyperemesis gravidarum who had received pyridoxine during her pregnancy. One sibling 6 years of age was entirely normal; however, the second pregnancy resulted in a full-term infant who developed generalized convulsions four hours after birth and succumbed within thirty hours. The convulsions in the case reported were controlled by intramuscular or oral administration of pyridoxine, singly or in combination with other vitamins, in doses varying from 2 to 6 mg. The seizures recurred at frequent intervals and could be made to recur when pyridoxine administration was discontinued for approximately fifty hours. The anticonvulsant effect of pyridoxine became evident as early as ten minutes after its administration. The electroencephalograms, which revealed grade I and II dysrrhythmias, likewise improved promptly after this vitamin. The cerebrospinal fluid protein of 80 mg per 100 cc. was unexplained. Because of the administration of pyridoxine during the pregnancy, and because xanthenurenic acid excretion tests failed to demonstrate a deficiency of pyridoxine, the authors designated this state as one of pyridoxine dependency. It is postulated that the administration of large doses of pyridoxine during the pregnancy resulted in an adaptive enzyme system capable of accelerating the breakdown of pyridoxine which manifested itself after birth in convulsions unless pyridoxine was regularly supplied above the normal dietary intake.

At the time of the writing this baby was 21 months of age, and was "depending" on 2 mg. of pyridoxine per day orally.

That a deficiency of pyridoxine can produce convulsions in humans and experimental animals appears well substantiated. This report postulates a most unusual example of a possible "adaptive" mechanism

developing in an infant causing an increase in the rate of pyridoxine destruction as a result of pyridoxine administration to the mother during her pregnancy. This postulation, as well as other possible causes and effects, offers an interesting and important challenge. The frequency of pyridoxine therapy in the management of hyperemesis without apparent undesirable sequelae leads one to believe that rare circumstances are present in this case. We shall await with interest similar observations in the literature.—J. N. ETTELDORF

Because pyridoxine deficiency is associated with a reduction in the level of circulating lymphocytes, further use of the principle of metabolic antagonists has been made in connection with the treatment of acute lymphatic leukemia by means of desoxypyridoxine.

The Effect of Pyridoxine Deficiency Induced by Desoxypyridoxine on Acute Lymphatic Leukemia of Adults. D. R. Weir and W. A. Morningstar, *Blood* 9: 173, 1954.

In this article the authors attempt to utilize the well-recognized lymphocytic depressive phenomenon of pyridoxine deficiency in treating humans afflicted with acute lymphocytic leukemia. The deficiency state was induced in four such patients by the use of the antagonist desoxypyridoxine. They found, as others have also, that a presumed deficiency could be attained on a "normal" diet if the dosage of the antagonist was high enough. However, they did not give any figures for xanthurenic acid in the urine after tryptophane, so that a chemical deficiency was not proved. Two of the four patients did develop seborrheic dermatitis, which can be taken only as presumptive evidence of vitamin B_6 deficiency.

The patients received variable amounts of desoxypyridoxine ranging from 400 to 1400 mg. per day. The results were erratic and difficult to evaluate. One patient experienced a hematologic remission in the peripheral blood after 51 days of therapy. However, relapse occurred in about one month and retreatment was without avail. In the other patients, less definite improvement occurred, and actually nothing occurred which might not have been compatible with the natural course of the leukemia.

The authors felt that the autopsy findings might be interpreted as showing some modification of the process by the induced deficiency state. In two of three cases, green crystals which produced foreign giant cell reaction were seen in the kidneys. These crystals remain unidentified. Futhermore, adrenal cortical degeneration, which could not be differentiated from post-mortem changes, was present.

The authors conclude that they observed enough clinical effectiveness from this form of therapy to pursue it further in other patients. Whether this opinion proves to be true, only time will answer.—J. F. MUELLER

STEATORRHEA

Steatorrhea arises from the impairment of the absorption of dietary fats by the small intestine. The fat absorption defect may arise from disturbances in biliary-pancreatic function, from specific diseases or anomalies involving the small bowel, or from the intolerance of the small intestine to certain factors in the diet, such as the gluten fraction of wheat. The mechanism by which jejunal insufficiency is produced by gluten is not known. However, recovery from celiac disease in children manifesting this sensitivity is effected by removing gluten from the diet.

Recent Trends in the Diagnosis and Treatment of Celiac Disease. C. M. Anderson. *M. J. Australia* 2: 211, 1953.

This paper is a summary of recent developments in celiac disease by an important worker in the field. Diagnosis of celiac disease is establised by fecal fat analysis, oral glucose tolerance curves, duodenal intubation, barium x-ray studies, and determination of chylomicronemia after a fatty meal. These changes are identical with those found in adult idiopathic steatorrhea.

Fifteen children with celiac disease were placed on a diet free of wheat or rye flour but otherwise were permitted to eat *ad libitum*. In each case, after several weeks on the diet the stools became normal in character and fat content; at the same time there was a noticeable clinical improvement.

In the experience of Dr. Anderson, a well-balanced diet is essential. Fats need not be restricted except early in the first few weeks in severe cases. At the present time, the mechanism by which gluten (the wheat or rye flour producing symptoms) acts is unknown.

The following foods are allowed: meats, fish, milk, fruits, vegetables, potatoes, rice, oats, butter, cheese, eggs, and sugar. Foods to be avoided are: bread, biscuits, pastries, cakes, many breakfast cereals, macaroni and spaghetti, and certain canned meats and soups containing wheat flour.—S. O. WAIFE.

That factors other than gluten may be responsible for idiopathic steatorrhea in the adult is apparent from the following significant observations.

The Influence of Gluten and Antibacterial Agents on Fat Absorption in the Sprue Syndrome. C. M. Anderson, A. C. Frazer, J. M. French, C. F. Hawkins, C. A. C. Ross, and H. G. Sammons. *Gastroenterologia* 81: 98, 1954.

The authors of this paper previously had made the fundamental observation that if wheat gluten were eliminated from the diet of children with celiac disease a prompt recovery would ensue. Re-introduction of whole flour or certain wheat protein

fractions resulted in a deterioration in the patients' condition.

An essentially similar situation exists in idiopathic steatorrhea and tropical sprue in adults. There is a depression in the absorptive capacity of the jejunum, an increase in mucus secretion, and dilatation of the intestine. These changes produced the characteristic roentgenographic appearance of the bowel. In addition, many of the changes in the stool can be attributed to increased bacterial activity and fermentation. In this study, 12 patients with idiopathic steatorrhea were placed on wheat-free diet for at least two months. Five subjects improved greatly; in 7 there was no significant change. Re-introduction of wheat protein into the diet of those who improved led to relapse. Thus, some subjects with idiopathic steatorrhea respond to wheat gluten as do children with celiac disease.

Other patients are either suffering from an entirely different disorder whose clinical picture is otherwise indistinguishable from idiopathic steatorrhea, or they are "sensitive" to some other factor(s) as yet unknown. In 3 cases of so-called tropical sprue, wheat gluten did not appear to be a primary causative factor.

Antibacterial therapy (sulfasuxidine, chloramphenicol, streptomycin, aureomycin) given *seriatim* and changing at 3- to 5-day intervals led to a definite improvement in the output of fecal fat in all the cases of sprue in which they were tried.—S. O. WAIFE

Studies on the Mechanism of Steatorrhea. C. Jiménez-Diaz, C. Marina, and J. M. Romeo. *Bull. Inst. Med. Res. Madrid* 6: 1, 1953.

The suspicion that an error of fat absorption is not the sole etiologic factor in idiopathic steatorrhea is confirmed by these observations on 44 cases of sprue-like enteritis.

Fecal fat content was estimated while the patients were ingesting either 6 or 30 Gm. of dietary fat per day; on certain days an additional 100 Gm. of fat was added, to test the effect of an excess of fat in the diet on fecal excretion. On the low fat diet, fecal fat excretion of some patients was equal to dietary intake, but in others, oddly enough, it was greater than the intake. When excess fat was fed, the results were inexplicably various: in many patients, the diarrhea and steatorrhea were aggravated, but this was *not* always the case; in some subjects, fecal fat showed *no* increase, and in a few instances it actually *decreased*. Since fecal fat output at times exceeded intake, it is suggested that faulty fat absorption cannot be the whole explanation. The authors posit secretion of a fatty fluid (chyle?) from the intestinal wall as a possible etiologic factor in some instances of idiopathic steatorrhea.—C.-J. HOWELL

The usual anemia encountered in association with idiopathic steatorrhea is of the hypochromic type, although macrocytic anemia has also been observed. The latter responds to the administration of folic acid. Impaired iron absorption and iron loss must be considered in the hypochromic type of anemia.

Iron Metabolism in Steatorrhea. J. Badenach and S. T. Callender. *Blood* 6: 123, 1954.

The anemia in idiopathic steatorrhea may be macrocytic with megaloblastosis of the bone marrow, but much more commonly it is hypochromic. However, good evidence of iron loss in the form of bleeding is lacking. The authors studied the problem of iron absorption in 16 patients with idiopathic steatorrhea, utilizing the technique of the radioactive iron absorption test. Utilization of iron in these patients was studied by means of intravenous radioiron. A control series of 15 patients with iron deficiency but without steatorrhea were similarly tested.

The results showed conclusively that the patients with idiopathic steatorrhea absorb much less iron than do patients without steatorrhea, but that the utilization of iron once absorbed is adequate. The effect of fasting and ascorbic acid on iron absorption was studied. Absorption was influenced only slightly in the case of fasting and not at all in the case of ascorbic acid.

The defect in iron absorption appears to have nothing to do with the amount of fat *per se*, since one patient with steatorrhea secondary to a gastrectomy absorbed very large amounts of radioiron. The authors suggest a hypothetical deficiency of apoferritin in steatorrhea accompanying an overall metabolic defect in protein as a cause for the poor absorption of iron.

However, even so, the authors were well aware of the necessity of considering iron loss in the causation of the hypochromic anemia. This would be particularly necessary in males, since the usual accepted daily loss of 1 mg., even with absolutely no absorption, would require several years to produce a hypochromic anemia. Therefore, although the poor absorption is of paramount importance in the refractoriness to therapy, it is only an additive factor in the etiology and one must assume some loss of iron to account for the hypochromia, namely, blood loss in one form or another.—J. F. MUELLER

Clinicians are aware of discrepancies between roentgenologic and bedside findings. This observation has been confirmed.

The Roentgenologic Appearance of the Small Intestine in Sprue. Long-term Studies with Special Reference to Differential Diagnosis. *Gastroenterology* 26: 548, 1954.

A series of 40 patients, consisting of 30 females between the ages of 26 and 75, and 10 males between

the ages of 36 and 67 years were completely studied and the diagnosis of sprue established.

Roentgen examination of the small bowel was carried out and frequent films were taken. Three patients revealed a normal small bowel pattern. Dilatation was found in 33, segmentation in 34, and scattering in 36. In 36 patients, transit time was between 3 and 5 hours.

Of particular interest was the fact that roentgen evidence of improvement in the sprue pattern occurred in very few of the patients who responded to antianemic or steroid therapy.

This marked discrepancy between the degree of clinical improvement and the roentgen changes reflecting that improvement warrants further investigation.—S. H. LORBER

LACTATION

Morrison recently published a monograph which showed how little reliable information we possessed about the yield and composition of breast milk ("Human Milk: Yield, Proximate Principles & Inorganic Constituents." Commonwealth Bureau of Animal Nutrition, Technical Communication No. 18, 1952). These papers, the first of a series, provide data which fill many of the gaps and are likely to cause considerable revision of ideas. No one interested in the subject can afford to ignore them.

Clinical and Chemical Studies in Human Lactation. F. E. Hytten. *Brit. M. J.* 1: 175, 176, 179, 249, 253, 912, and 1410 (1954).

I. Collection of Milk Samples (p. 175).

Milk composition varies from feed to feed and during the course of a single feed, and only complete 24-hour samples are likely to give a true picture of composition at a given stage of lactation. It is shown that a recently-devised mechanical breast pump—the "humalactor"—permits collection under conditions which disturb the normal process very little, and extracts milk more completely than manual expression.

II. Variations in Major Constituents during a Feeding (p. 176).

By the use of the humalactor, it is possible to collect serial samples during the course of emptying the breast without interrupting the process. Most patients studied were in the first week of lactation, but one was studied several times between the 7th and 23rd days. During the course of a "feeding," the fat content of milk usually rises progressively and by a large amount; concurrently, the lactose content tends to diminish. During the first few days of lactation, the total nitrogen content tends to fall during the course of a feeding, but as the milk becomes more mature this trend is reversed, owing to a relative rise in casein concentrations. An ingenious experiment enabled the changes to be reproduced *in vitro*, and suggests that the changing fat composition during a feeding is due to adsorption of fat globules onto the secretory and duct surfaces of the mammary glands, the changes in other constituents being secondary to this.

III. Diurnal Variation in Major Constituents of Milk (p. 179).

There are considerable diurnal variations of yield and fat content, especially during the first week of lactation. These early variations do not seem to follow any consistent pattern. Later in lactation, there is a relatively high yield and fat content, at the 10 a.m. feed. Why the fat content varies from feed to feed is unknown. Variations of yield may be related to the length of time since the last feed and the storage capacity of the beast. Haphazard but comparatively small variations of lactose content were observed. Variations of nitrogen content were insignificant in relation to the rapid fall which occurred during the first week; this was so marked that the nitrogen content during the first few days tended to drop from one feed to the next.

IV. Trends in Milk Composition during the Course of Lactation (p. 249).

Most observations were made during the first two weeks. At first, the 24-hour yield is small but rises rapidly from the point where, clinically, the milk "comes in." Individual variations of yield were so great that no attempt was made to construct an average curve. During the first three days, the total nitrogen output dropped rapidly, then flattened out rather abruptly at a level which continued to diminish slowly until about the second month. The lactose content rose during the first week, but values fluctuated considerably in the same subjects, contrasting with the regularly progressive values for nitrogen content. An average curve of fat content could not be usefully constructed, as variations between individuals were great; but repeated observations on the same subjects indicated a slow but irregular rise at first, reaching a more stable figure about the end of the first week. The 24-hour fat output rose progressively during the first week; the variations of fat content were due to gross variations of milk volume. By the 7th day, however, fat content levels were stable enough to indicate fairly accurately the fat content of the mature milk in each case. Lactose and nitrogen contents in 7th-day milk tended to be inversely correlated; thus, if the milk on the 7th day has a low lactose content, it will almost always have a high protein content and the milk secretion as a whole will resemble that of earlier lactation. The lactose content of mature milks varied little, and the average value of 6.9 Gm. per 100 ml. may be a physiological norm for the human.

V. Individual Differences in Composition of Milk (p. 253).

Most data in the literature are unreliable, owing to the use of inadequate methods of sampling milk,

or because unrepresentative subjects, such as professional wet-nurses, have been studied. In the present enquiry, the 24-hour output on the 7th day of lactation was collected from 150 unselected hospital patients, 121 of whom were primiparae. Although the milk of the multiparae did not differ significantly from that of primiparae, a comparison of milks produced by the same patients in a first and in a subsequent lactation (6 cases) showed wide differences of fat content between lactations. Since the effect of parity is incompletely understood, analyses were restricted to data from 121 primiparae. The following results were obtained:

	Coefficient of variation	%
Volume	414 ± 172 ml.	41.5
Fat	3.17 ± 0.78 Gm./100 ml.	24.6
Lactose	6.29 ± 0.45 Gm./100 ml.	7.2
Total nitrogen	296 ± 38 mg./100 ml.	12.8
Protein	1.44 ± 0.22 Gm./100 ml.	15.3

The mean calorie value (578 ± 73 per liter) was closely dependent on the fat content. Volume and fat values showed a normal distribution; lactose and total nitrogen distributions were slightly skewed, in a manner which suggested a physiological upper limit to lactose content and a lower limit to nitrogen content. Correlations between values showed that fat content is virtually unpredictable without direct analysis; on the other hand, milk produced in large volume tends to have a high lactose and low protein content, and vice versa. The high variability of volume and fat content (and hence of fat output) is maintained throughout lactation, and calculation suggests that about 20 per cent of women will produce a mature milk with a calorie value of 570 calories or less per liter. "Assuming that these women are capable of producing a litre of milk daily . . . and assuming that the calorie requirements of the infant are 115 calories per kg. bodyweight . . ., then one-fifth of the lactating population will be incapable of adequately nourishing an infant beyond a weight of 11 lb. (5 kg.). The mother who explains her lactation failure by saying 'my milk was too thin' may, in fact, be telling the truth." The findings contradict the widely held belief that the composition of milk varies very little.

VI. The Functional Capacity of the Breast (p. 912).

Whether the size of the breast is related to the yield and composition of the milk it produces is doubtful; breast size is not necessarily related to the amount of functional tissue. Breast sizes were determined by a method of water displacement, and the results related to the analyses of 24-hour samples of 7th-day milk. There was a small correlation between breast size and milk yield ($r = +0.3$ approx.) but none between size and fat, protein, or lactose content. It is likely that the increase of size of breasts during pregnancy is related to growth of secretory tissue, and data from 9 primiparae and 2 multiparae suggested strongly that those whose breast sizes increased most between the 3rd month of pregnancy and the 7th day post-partum had the highest milk yields, and vice versa. The correlation between the pregnancy enlargement of the breast and its output on the 7th day post-partum gave a coefficient of +0.87, significant at 1%. The data suggested, further, that younger primiparae had greater breast enlargement and higher milk yield than older; this difference, if confirmed, may be due to "disuse atrophy" of breast tissue in elderly primiparae. Twenty per cent of the patients reported breast symptoms during menstrual periods, and these showed greater pregnancy increase of breast size and greater milk output than those who reported no breast symptoms during menstruation. Subjective impressions of breast growth or "tension" during pregnancy were too unreliable to have any prognostic value.

VII. The Effect of Differences in Yield and Composition of Milk on the Infant's Weight Gain and the Duration of Breast Feeding (p. 1410).

The terms "lactation" and "breast-feeding" must be differentiated. Lactation is a largely automatic physiological function showing wide individual variation; successful breast-feeding depends on adequate lactation, but the converse is by no means necessarily true. Of 167 women whose milk was sampled on the 7th day of lactation, 148 could be followed up for 13 weeks. Where necessary, the reasons for stopping breast-feeding were determined. The growth in weight of the babies was determined in 83 cases who attended child welfare clinics. Breast-feeding progress and infant growth were related only to milk yield and fat content, the product of which is fat output. Where the fat output on the 7th day was less than 5 Gm., 40 per cent of the infants lost weight or required complementary feeds, and only 20 per cent gained more than 4 oz. between the 3rd and the 7th days of life. As fat output increased, the babies gained more weight and fewer required complementary feeds. Similarly, there was a highly significant relationship between fat output and weight gain during the first 4 weeks; this did not hold at later stages. The position is, however, obscured by the fact that most mothers with a low fat output quickly ceased to breast-feed. Of the 148 patients whose breast-feeding histories were known up to the 13th week, 23 gave up for reasons unconnected with adequate lactation. In the remaining 125, there was a marked relationship between fat output on the 7th day and the duration of breast-feeding. Although fat output gave the best indication, yield alone was of considerable prognostic value. Of those mothers who produced at least a pint (570 ml.) of milk on the 7th day, 81 per cent breast-fed for at least 3 months. Milk which is slow to "come in" does not necessarily portend unsuccessful breast-feeding.—F. E. Hytten

ANEMIA

The following discussion of the treatment of anemia should be read in its entirety by all medical practitioners, many of whom are too inclined to use polyhematinic preparations.

Principles in the Management of Anemias. M. M. Wintrobe. *Bull. New York Acad. Med.* 30: 6, 1954.

Successful treatment of anemia is dependent upon an accurate diagnosis of the condition and information as to the underlying disorder resulting in the anemia.

Anemias can be divided into four etiological classes: (1) Anemia caused by blood loss. (2) Anemia resulting from deficiency of materials essential for red cell construction. This may involve deficiencies of iron, copper, cobalt, vitamins such as vitamin B_{12}, folic acid, pyridoxine, niacin, possibly riboflavin, pantothenic acid, and thiamine. The requirements for several of these substances are so low that the chances of an anemia developing through a deficiency of one of them is unlikely. Storage in the body and intestinal bacterial synthesis serve as safety factors against depletion. (3) Anemia developing through increased blood destruction. This type of anemia may be due to several causes, e.g. infectious chemical agents, immune body reactions, hereditary spherocytosis. (4) Anemia due to impaired production of red corpuscles. This may be a congenital or hereditary anemia in nature, or one acquired with such conditions as infection and chronic renal disease.

The differentiation of the various types of anemia can be achieved by an adequate history and physical examination which would include a thorough study of the patient's blood.

For effective management it is necessary to have an accurate diagnosis. The number of true therapeutic agents is small, the only truly specific ones being iron and vitamin B_{12}. Other agents which might be included are folic acid, desiccated thyroid, and possibly ascorbic acid. Nonspecific therapeutic agents would include blood transfusion, splenectomy, and the hormones, corticotropin (ACTH) and cortisone.—M. W. Bates

Severe iron deficiency anemia, accompanied by dysphagia, occurs characteristically in women, and has been termed sideropenic dysphagia. Two patients are reported, one of whom, interestingly enough, recovered without the administration of iron.

Syndrome of Anemia, Dysphagia and Glossitis (Plummer-Vinson Syndrome). J. T. Howell and R. W. Monto. *New England J. Med.* 249: 1009, 1953.

An iron-deficiency anemia, formerly called the Plummer-Vinson syndrome, accompanied by dysphagia and glossitis, found in women aged between 40 and 50 years, is now known as "sideropenic dysphagia." The anemia, usually moderate in degree, is microcytic and hypochromic. Achlorhydria is often found, but no more often than in the usual iron deficiency anemia. The tongue is usually devoid of papillae. The dysphagia is localized to the cricoid area of the neck. X-ray and esophagoscopic examinations show longitudinal folds and obstructive webs in the introitus of the esophagus.

Two cases are reported in which recovery was brought about by two different treatments. In one, intravenous administration of iron was used. In the second, recovery was effected by a hyperalimentation technique unsupplemented by iron or vitamins.—M. W. Bates

Although a majority of patients with hypochromic anemia will respond to oral iron, it is true that the administration of vitamin C in conjunction with iron preparations will reduce the incidence of gastrointestinal distress. There is considerable doubt, however, as to whether ascorbic acid will increase the availability of iron for absorption.

The Treatment of Hypochromic Anemia with a Compound Containing Ferrous Sulphate, Vitamin C and Vitamin K. R. O. Gillhespy. *Med. Press* 231: 112, 1954.

Quite a few cases of hypochromic anemia fail to respond to any of the traditional forms of oral iron therapy. In some, gastrointestinal irritation may prevent adequate absorption of the iron; other patients may simply be refractory to all forms of iron therapy. The author feels that the first group can be considerably reduced by the use of a preparation combining the ferrous sulfate salt with vitamins C and K.

The new compound was administered only to patients with uncomplicated iron-deficiency anemia. Some 120 patients received one tablet (containing approximately 200 mg. ferrous sulfate) three times daily for periods of 3 weeks to 6 months. After about 16 months, the results were evaluated; 53 cases were considered suitable for assessment of the hematopoietic effectiveness of the compound, and 109 were selected for evaluation of the incidence of gastrointestinal symptoms. Of the 53 cases, 46 achieved normal hemoglobin concentration within "a reasonable length of time"; 7 were not benefited. Only 2 complained of side-effects—dryness of the mouth and dizziness in one instance, nausea in the other. Patients who failed to respond to this treatment subsequently proved refractory to other oral iron preparations and had to be given intravenous iron. In all, 109 persons received the compound without gastrointestinal disturbances of any sort; 12 patients who had previously been intolerant to oral iron had no gastrointestinal symptoms while receiving this compound; only one patient complained of gastrointestinal dis-

tress—hardly significant when one considers the incidence of indigestion.

The author believes ferrous sulfate combined with vitamins C and K to be the least toxic of all available iron preparations and recommends it as the preferred treatment for hypochromic anemia.—C.-J. HOWELL

ITEMS OF GENERAL INTEREST

Current Research in Nutrition. R. E. Olson. *J. Am Dietet.* A. 30: 111, 1954.

This is an excellent review, with extensive bibliography, which considers past, current, and possible future developments in nutrition research. In the opinion of the author, the scope of nutrition is broad, for a study of food brings into focus such disciplines as agriculture, geography, soil chemistry, economics and marketing, social anthropology, food technology, cookery, and dietetics. Psychology, psychiatry, biochemistry, physiology, pathology, microbiology, endocrinology, hematology, and several other "ologies" come into play in a study of the relationship of food to life.

Historically, nutrition can be categorized as a play in four acts. The first act or "age of the single nutrient"—calories or energy—begins the drama. Hippocrates in 400 B.C. recognized food as a source of energy. Galen, Sanctorius, Lavoisier, Mulder, and Liebig are the "stars" in this act, which lasted until 1840 A.D. The age of "the four nutrients," lasting until 1912, comprises the second act. Act three, the age of "multiple nutrients," was introduced by the work of Hopkins, in 1912, who showed that four purified nutrients would not sustain growth in the rat. Today we recognize some fifty purified nutrients which collectively support growth and development in animals. The author believes that the age of identifying and purifying new growth factors is nearly over and act three is drawing to an end. The set for act four was laid when Warburg in 1932 discovered that trace nutrients are key molecules in the enzymatic structure of cells.

Important areas of current research are (1) the calorie problem, and (2) vitamin-enzyme-hormone relationships. The hazards of obesity, diet plans for weight reduction, and appetite causation have been studied extensively. No one has undertaken investigation of amino acid levels in connection with appetite and obesity, despite the fact that glutamic acid is rapidly oxidized by cerebral tissue.

The second area of research—that of relationships—has made great advances. Most of the vitamins of the B-complex have been shown to function as co-enzymes. The most recent vitamin to be added to the list of co-enzymes is *pantothenic acid.* In the author's laboratory, a study of the origin of the sulfur-containing moiety of co-enzyme A suggests it is derived from cystine. In the area of endocrine-nutritional relationships, for example, it has recently been shown that alloxan diabetic rats do not convert thiamine to cocarboxylase at a normal rate.

The problem of nutrition in chronic disease in man is an area for research which badly needs attention by nutritionists. We have only a glimpse of the nutritional requirements of patients with heart failure, arteriosclerosis, cancer, rheumatoid arthritis, sprue, ulcerative colitis, cirrhosis of the liver, diabetes, and other chronic metabolic, vascular, or neoplastic disorders.

It is now possible, by means of cardiac surgery, B-complex deficiency diets, and thyroid excess, to induce sufficient myocardial or valvular damage in dogs to produce typical congestive heart failure. Studies now in progress in the author's laboratory designed to elucidate changes in nutritional requirements as animals develop advanced congestive heart-failure are to be paralleled with studies on cardiac patients.

It is predicted that an era of therapeutics may develop when dietary management will include trace metals and specific amino acid supplementation or restriction. Specific ratios of nutrients may be important in disease management. Public health nutritionists will need to be familiar with the lesser as well as the greater members of the B-complex, and "a sound knowledge of nutrition will become more important in the practice of medicine and public-health as the years pass."—J. M. SMITH

A Single Diet for All Living Organisms. T. D. Luckey. *Science* 120: 396, 1954.

Although man and other animals eat different foods and species of mammals differ widely in their food habits, there is a similarity in the basic essential ingredients. In an attempt at finding a single diet formula applicable to all organisms, a semisynthetic "universal diet" was prepared.

The diet contained vitamins in excess, and consideration was given to the salt requirements of chicks and guinea pigs, the fiber requirements of rabbits, fat intake of dogs, etc.

In terms of grams per kilogram of diet, the composition was: purified casein 300, corn oil 80, cornstarch 300, cellulose 120, sucrose 120, NaCl 3.0, other minerals and vitamins as described in the text.

Certain limitations have since become apparent. Unknown constituents may be present in casein or corn oil, and hematin, cholesterol, thioctic acid (alpha-lipoic acid) and purines were not added.

Satisfactory growth rates were obtained when this diet (altered only in physical characteristics) was fed to monkeys, pigs, cats, dogs, rats, mice, rabbits, and guinea pigs, in addition to other animals. Certain micro-organisms, including *E. coli, Tetrahymens gelleii,* and *L. arabinosis,* were maintained in pure culture through several transfers, and even goldfish, snails, and tomato plants grew on this regimen.

The concept of a universal diet would appear to be fruitful in biologic research, in that its use would eliminate one complex variable; it might facilitate the search for new nutrients and be an important tool in comparative biochemistry.—S. O. WAIFE

Modification of the Choline Deficiency Syndrome in the Rat by Somatotrophin and Hydrocortisone. C. E. Hall and J. G. Bieri. *J. Endocrinology* 59: 661, 1953.

Griffith and Wade in 1939 described the syndrome of fatty infiltration of the liver and hemorrhagic necrosis of the renal cortex occurring as a consequence of a choline-deficient diet in the immature rat of 21–23 days of age. Cortisone and Upjohn Lipo-Cortex Extract protect rats against the renal changes and, to a lesser extent, against the fat infiltration of the liver. The present paper reports upon the effects of somatotrophin ("growth hormone") and hydrocortisone.

The experimental series consisted in the following: Group I—rats on a choline-deficient diet (called basal diet); Group II—basal diet plus 0.2 per cent choline; Group III—diet same as Group II plus 1.25 mg. of somatotrophin subcutaneously twice daily; Group IV—basal diet plus somatotrophin as in Group III; Group V—basal diet plus 2.5 mg. somatotrophin twice daily; Group VI—basal diet plus 1 mg. hydrocortisone once daily subcutaneously.

After six days the animals were sacrificed. It was found that in the choline-deficient animals somatotrophin increased the incidence and severity of the renal damage but did not increase liver fat. No somatotrophic effects were noted. Somatotrophin in animals on a normal diet promoted growth and exerted no toxicity. Hydrocortisone prevented the choline deficiency lesions from occurring in the kidney but did not prevent the fatty infiltration of the liver.

These observations suggest that choline requirements may be increased in the growth hormone-treated animals and thereby an intensification of the renal lesion occurred. It is surprising, however, that no intensification of the hepatic lesion was noted in view of the previously described effects of growth hormone on fat transport. Hydrocortisone inhibited the growth of the choline-deficient animals, and perhaps relatively diminished the choline deficiency. The failure to modify the hepatic lesion may be related to the described effects of adrenal steroids upon fatty infiltration of the liver seen in non-choline-deficient animals.—L. RECANT

Clinical Evaluation of a High-Protein, High-Carbohydrate, Restricted-Fat Diet in the Treatment of Viral Hepatitis. N. C. Leone, F. Ratner, W. C. L. Diefenbach, M. G. Eads, J. E. Lieberman, and R. Murray. *Ann. New York Acad. Sc.* 57 (art. 6): 948, 1954.

A group of volunteer subjects were infected with the agent(s) of virus hepatitis. Early in the course of their disease, six patients were divided into two groups: one received a well-balanced diet of approximately 4000 calories (at least 200 Gm. protein, 75 Gm. fat, and 680 Gm. carbohydrate); the other group was left alone and had a typical institutional "ad lib" diet.

During the acute phase, those on the special diet had an average intake of 3600 calories, 203 Gm. protein, and 78 Gm. fat, while those on the *ad libitum* diet ingested 1400 calories and 125 Gm. protein less. The fat intake was the same. Approximately similar results were obtained during the recovery phase, except that the *ad libitum* intake contained about 18 Gm. more of fat.

Taking the return of serum bilirubin to 1.0 mg. per 100 ml. as an endpoint of recovery, the course was 23 days longer for the subjects on the special diet as compared to the *ad libitum* group. Furthermore, the occurrence of complications was more frequent among patients receiving the high protein and carbohydrate, restricted fat diet.

This study should make us re-evaluate the "evidence" that a high protein (and low fat) intake is essential to the recovery from hepatitis. Certainly more studies of this type are needed.—S. O. WAIFE

Children with and without Rheumatic Fever. I. Nutrient Intake, Physique, and Growth. E. B. Wilcox and L. S. Galloway. *J. Am. Dietet. A.* 30: 345, 1954.

This paper presents a comparison of dietary and height-weight data for 131 children (5–19 years of age) with a history of rheumatic fever with those for 131 children of the same age and sex and no history of this disease. Seven-day dietary records were obtained for each subject between July and November 1950. Height and weight measurements of the children were made during the following week. Results of blood analyses and medical examinations made at the same time will be reported later.

In comparing the findings, data for boys and girls were grouped separately and each sex was divided into four age groups: 5–9; 10–12; 12–15; and 13–19 years. In every instance rheumatic and control children were compared. Diets were assessed on the basis of the average daily intake of ten nutrients. Weights and heights were compared to Baldwin Wood, Stuart and Meredith, and Wetzel standards.

The findings were summarized as follows: "The girls in the non-rheumatic group were consuming significantly more calories, protein, fat, iron, thiamine, and niacin than those in the rheumatic fever group. Differences between the intakes of the two groups of boys were not significant. Differences between the intakes of the girls and boys of various age groups were not significant for most of the nutrients.

"The children under ten years of age were consuming adequate diets when average values were compared with the Recommended Dietary Allowances. The older children had intakes of ascorbic acid below the allowances, and the older girls also had lower intakes of other nutrients except for vitamin A and riboflavin.

"Low intakes of calcium, iron, and ascorbic acid were found for many of the older boys and girls. The thirteen- to fifteen-year-old girls of the rheumatic fever group were consuming less calcium and iron than other groups while the older boys and girls of the control group had the lowest intake of ascorbic acid.

"Slightly more of the children in the rheumatic fever group tended to be underweight and were in the physique channels of the Wetzel grid which represented borderline or poor physique and growth than were found in the non-rheumatic group.

"More of the boys with good physique and growth met the daily allowances for all nutrients except for ascorbic acid than did those with poor growth. Similar numbers of girls with either good or poor growth were meeting the daily recommended allowances or two-thirds of them."—J. M. SMITH

Children with and without Rheumatic Fever. II. Food Habits. E. B. Wilcox and L. S. Galloway. *J. Am. Dietet. A.* 30: 453, 1954.

This reports a comparison of the food habits of 131 children 5 to 19 years of age and with a history of rheumatic fever with habits of 131 children without such a history. The rheumatic and nonrheumatic were paired as closely as possible in age, sex, and economic status. Both groups were drawn from the Ogden, Utah area. Details concerning the conduct of the study were reported earlier.

In this paper, kinds and amounts of foods eaten are studied. For boys and girls 5–9, 10–12, and 13–19 years of age, comparisons are made between rheumatic and nonrheumatic children in average daily consumption of milk; eggs; meat, fish, and poultry; other protein foods; potatoes; green and yellow vegetables; other vegetables; citrus fruits; tomatoes; bread; cereals; butter or margarine; candy, soft drinks; jam, jelly, sugar; and desserts.

Average daily intakes of the various foods were similar for both groups. The mean intake of milk amounted to two cups or more for all groups, with adolescent boys using three. Fifty-seven per cent of the adolescent girls in the rheumatic fever group used less than two cups of milk daily. The calcium intake of many of the girls in this group was therefore low. More boys than girls in both groups were using three cups or more of milk. All groups averaged approximately one or more servings, daily, of meat, poultry, and fish, and used three to five eggs per week. The intake of green and yellow vegetables and of citrus fruits and tomatoes did not each equal one serving daily for most of the children. The ascorbic acid content would have been improved by higher intakes of tomatoes, citrus fruits, cabbage, and cantaloupe.

The foods disliked by the most children were cabbage, spinach, peas, liver, and eggs.

When the food intake of the rheumatic fever children was compared with the recommendations of Jackson and Kelly (*J. Am. Dietet. A.* 251: 392, 1949) for rheumatic fever therapy, less milk, eggs, citrus fruits and tomatoes, and vegetables other than tomatoes were being used than recommended. Jackson and Kelly had recommended the daily use of one quart of milk; one or two eggs; one serving of meat, fish, chicken, or liver; two servings of vegetables; one orange, apple, or tomato or other fruit; one teaspoon cod liver oil; six teaspoons butter or margarine; and other foods such as bread, cereal, and potatoes to satisfy appetite and maintain correct weight.

According to the data reported for these 262 children, there were no great differences between diets of rheumatic and nonrheumatic children of similar age, sex, and economic status. It was suggested by the authors that the children with rheumatic fever may have improved their diets after diagnosis of their disorder. There is no way to tell from this study the extent to which poor nutrition may have been a factor in the onset of the disease.—J. M. SMITH

"Acid" Phosphatase in Niemann-Pick's Disease and a Therapeutic Experiment with Cortisone. B. Hastrup and A. Videbaek. *Acta med. Scandinav.* 149: 287, 1954.

Niemann-Pick's disease is a rare anomaly of phospholipid metabolism. Little is known about these derangements. The serum of a three-year-old boy with the disease contained a large amount of an "acid" phosphatase. The optimum pH of this enzyme was about 5. Unlike the acid phosphatase found in prostatic cancer, this phosphatase was almost unable to split glycerophosphate. Cortisone did not alter the downhill course of the disease, the serum concentration of lipids, nor this "acid" phosphatase. —S. O. WAIFE

Myotatic Irritability. W. T. C. Berry. *Brit. J. Nutrition* 8: 165, 1954.

The subjects of the investigation were 105 men, all more or less lean, who were examined in January, March, and October 1949. The reaction was elicited by holding the biceps muscle firmly between thumb and index finger and subjecting it to a single plucking pinch. The subject remained standing, his arm hanging comfortably at his side. In cases recorded as positive a contraction ring arose, after a slight delay, along the line of contact with the thumb and finger.

A relationship is described between myotatic irritability and the amount of body fat in 105 men studied during and after the blockade of Berlin in 1949. An equivocal response was observed to treatment with thiamine, in contrast to reports of its efficacy by other workers. Persistence of the sign in curarized muscle showed that the site of its excitation was distal to the neuromuscular junction. It is suggested that myotatic irritability is most marked when the muscle is easily compressed; undernutrition, curarization, and thiamine deficiency have this in common—that in all of these conditions the muscles are soft to touch and easily compressed.—B. Sure

Developing Breads of Higher Nutritive Value. V. B. Parks, E. M. Hewston, M. W. Marshall, and A. M. Bruinooge. *J. Am. Dietet. A.* 30: 245, 1954.

This paper reports results of efforts to develop highly acceptable breads of the "homemade" type which would also be high in calcium, protein, and thiamine. The thiamine content was of particular concern, since earlier studies of seventy school meals as served to fourth and sixth grade pupils had shown that eight of the meals contained less than one-fifth the recommended dietary allowance of thiamine, and only twenty-two contained as much as one-third the allowance. Large-quantity and commercial formulas were developed for six breads—white, raisin, whole wheat-white, soy-white, soy-wheat germ-white, and brewers' yeast-white. These were rated for quality in the laboratory by a panel of six trained judges, and by school children when five of the breads were prepared by school cooks.

The whole wheat-white (50% patent flour, 50% whole wheat, 6% nonfat dry milk) was rated highest by the judges. The soy-wheat germ-white (3 lb. full fat soy, 3 lb wheat germ and 6 lb. nonfat dry milk per 100 lb. flour), though rated highest by some judges, had the lowest total score. In the schools, a check on plate waste showed that the percentage of pupils leaving no bread or almost none was: "raisin," 97%; "white," 95%; "whole wheat-white," 91%; "soy-white," 87%; and "soy-wheat germ-white," 78%.

Assayed calcium content of laboratory baked bread was 2–13% higher than the calculated value for four of the breads. The raisin bread fell 4% below the calculated value. Assayed thiamine was 4–29% below the estimated content for five of the breads. The thiamine content of the brewers' yeast-white bread was 33% above the estimated content.

For the six breads, calcium/lb. ranged from 270 to 434 mg. The higher values were found when 10% milk solids were used. Previous analyses by the authors of commercial white breads showed calcium contents of 54 to 694 mg. per pound with an average of 334 mg. per pound.

The analyzed thiamine content of the six laboratory breads ranged from 0.98–2.60 mg./lb. Thus the white, raisin, and soy-white breads (0.98, 1.03, 1.05 mg./lb., respectively) fell below the Food and Drugs Administration's Definitions and Standards of Identity of 1.1 mg. per pound.

Five formulas, containing 6–10 per cent milk solids, have been published for commercial use (U.S.D.A. Program Aid No. 185, October 1951). These formulas specify use of unenriched flour and enrichment wafers to assure bread with thiamine levels that meet federal standards for enriched breads. The authors recommend this practice in large commercial bakeries. Since this will ensure against low thiamine values when the relative amount of flour is reduced by additions of yeast, milk solids, raisins, or other ingredients in an effort to raise the protein or calcium content of breads.—J. M. Smith

The Fortification of Bread with Lysine. III. Supplementation with Essential Amino Acids. H. R. Rosenberg, E. L. Rohdenburg, and J. R. Baldini. *Arch. Biochem. & Biophys.* 49: 263, 1954.

Using a basal bread diet (12.5 per cent protein) which contained 90 per cent dry bread as the only source of protein and carbohydrate, an average weight gain of 54 Gm. was obtained in weanling rats in five weeks. This compared with weight gains of approximately 175 Gm. on a stock diet which provided 21.5 per cent protein, or on the basal bread diet plus 0.8 per cent of lysine.

Comparison of the essential amino acids in bread with that believed to be required by the rat indicated that bread might also be deficient in methionine, valine, and threonine. The addition of these three amino acids to lysine-supplemented bread diets did not produce any beneficial effects on the growth of rats, and it was concluded that so far as rat growth was concerned, only lysine is deficient in commercial white bread.—M. K. Horwitt

Effects of Partial Replacement of Rice in a Rice Diet by Tapioca Flour on the Metabolism of Nitrogen, Calcium and Phosphorus in Adult Human Beings. H. B. N. Murphy, M. Swaminathan, and V. Subrahmanyan. *Brit. J. Nutrition* 8: 11, 1954.

Six healthy adult males who carried out ordinary duties in the laboratory were chosen as experimental subjects. They were first clinically examined and found free from any disease. They were housed in a building specially designed for human metabolic studies and were kept under strict supervision during the experimental period.

The metabolism of nitrogen, calcium, and phosphorus was studied in the six men fed on diets based on rice and on a mixture of 75 per cent rice and 25 per cent tapioca. The composition of the rice diet was similar to that ordinarily consumed by people belonging to the low-income groups in many parts of India. The average daily intake of nitrogen on the

rice diet and the rice-tapioca diet was 9.69 and 8.93 Gm., respectively. In spite of a slightly lower nitrogen intake on the rice-tapioca diet, the average retention of nitrogen on the two diets was 2.65 and 2.75 Gm., respectively.

Four of the six experimental subjects were in positive calcium balance and two in negative balance on the rice diet. All the six subjects were in positive balance on the rice-tapioca diet. The average daily retention of calcium was 47.2 mg. on the rice diet and 153.4 mg. on the rice-tapioca diet. The average daily intake of phosphorus was nearly of the same order on both diets. The average absorption of phosphorus was only 43 per cent on the rice diet as compared with 60 per cent on the rice-tapioca diet. The daily average retention of phosphorus was 196 mg. on the rice diet and 470 mg. on the rice-tapioca diet.—B. SURE

Effects on the General Health and Nutritional Status of Children of Partial Replacement of Rice in a Poor Vegetarian Diet by Tapioca Flour. S. K. Reddy, T. R. Doraiswamy, A. N. Sankaran, M. Swaminathan, and V. Subrahmanyan. *Brit. J. Nutrition* 8: 17, 1954.

The subjects were girls 4 to 12 years old who were residents in an orphanage. The children were examined clinically and those free from diseases were included. Routine de-worming was done in order to eliminate possible disturbances in the digestion and absorption of food.

A feeding experiment lasting six months was carried out to evaluate the effect on growth and nutritional status of these children of replacing 25 per cent of the rice in a poor vegetarian rice diet by tapioca flour. Data on the weight, height, hip width, hemoglobin, red blood cell count, and serum proteins were obtained at the beginning and at the end of the experiment for a group of children receiving the rice-tapioca diet and for a control group of similar children receiving the rice diet. The results showed that there was no significant difference between the two groups with respect to any of the characteristics studied, with the exception of hemoglobin. Though the hemoglobin content of the blood decreased in both groups, the decrease was significantly less ($P < 0.005$) in the experimental group than in the control group.—B. SURE

Gain in Weight and Length in the First Year of Life of Chinese Infants Born in Singapore in 1951. J. Millis. *Med. J. Australia* 1: 283, 1954.

Regular visits were made to the homes of 73 male and 55 female "full-term, normal" Chinese infants of lower income group families; 2055 observations of weight and 337 of length were recorded during the first year and age-weight curves were constructed. The gain in weight of Chinese infants was similar to that of Caucasian infants for the first twenty weeks of life, but after six months of age the increase was noticeably slower.—AUTHOR

Nature of the Pressor Response Induced by Cortisone in Potassium-Deficient Rats. S. C. Freed, R. H. Rosenman, and M. K. Smith. *Am. J. Physiol.* 178: 85, 1954.

Potassium-deficient diets lower blood pressure both in controls and in renal hypertensive rats. These pressures are restored by cortisone acetate. It is suggested that cortisone replaces an endogenous deficiency of cortical secretion which results from potassium restriction. After adrenalectomy a moderate hypertension is produced by cortisone if potassium intake is adequate.—M. J. OPPENHEIMER

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